CIRRHOSIS of the LIVER

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LIVER

By

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Dedicated to my Father

Martin S. Kleckner, M.D., F.A.C.S.,

whose advice and encouragement were responsible for the prepera-tion of this manuscript.

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FOREWORD

THIS IS A LARGE volume covering the subject of cirrhosis of the liver in its historical, experimental, pathologic and clinical aspects. It is designed primarily for the busy clinician and will serve as a ready reference for help in evaluating the clinical aspects of the cirrhotic patient and provides an adequate bibliography for those who wish more intensive perusal and study of the work referred to in this monograph. Doctor Kleckner's efforts to summarize the problem of cirrhosis in this volume do justice to his boundless energy and enthusiasm.

J. ARNOLD BARGEN, M.D.

ARCHIE H. BAGGENSTOSS, M.D.

PREFACE

This book has been written especially for the use by the clinician. It is intended to serve a dual purpose. First, an attempt was made to review and organize important and recent aspects of cirrhosis selected from the medical literature throughout the world. Secondly, it reports on certain aspects of cirrhosis that have most interested the author. The first endeavor was a particularly difficult assignment. Only within recent years has there been general agreement of the morphological features of cirrhosis. Cirrhosis originally had been considered to be a discolored, fibrotic, sclerotic, or often an atrophic liver. Consequently many reports of cases and classifications of cirrhosis published in the literature were either inadequately documented, or, as in the instance of experimental cirrhosis in animals, bear little or no relation to the human type.

This book is not intended to describe at great length the morphological features and functions of the liver. The structure of the normal liver and the morphogenesis of cirrhosis have been reinterpreted within the last few years, whereas the many functions of the liver require further investigation. If possible, the term cirrhosis is employed in this book only where there is indisputable morphological evidence obtained by needle biopsy of the liver or at necropsy of nodular regeneration, fibrosis, in particular, and hepatocellular regeneration.

The chapters have been arranged in order to describe the fundamentally important morphogenetic concept of cirrhosis, to discuss the pathological and clinical features of the different types of cirrhosis, and specific diseases associated with cirrhosis and to appraise and treat the three general patho-physiological aspects of cirrhosis, namely portal hypertension, ascites and hepatic insufficiency. The title of the book emphatically implies a very complex subject. Cirrhosis is considered at best as a pathological entity, characterized by innumerable metabolic disturbances, a

few cardinal physical findings, and generally, nondescript symptoms.

The preparation of this book would have been impossible without the generous assistance and constructive criticisms of many colleagues. My interest in diseases of the liver was kindled initially during my fellowship at the Mayo Foundation and Mayo Clinic. For this reason I am particularly indebted to the staff of the Sections of Medicine (Gastroenterology) and Pathological Anatomy of the Mayo Clinic. The facilities and records of the Ochsner Clinic, Ochsner Foundation Hospital, Tulane University School of Medicine, and Charity Hospital of New Orleans provided much of the pathological and clinical material. I am deeply indebted to the Department of Dietetics of the Ochsner Clinic and Foundation Hospital for providing some of the diets listed in Chapter 17. The efforts of Miss Selma DeBakey, Editorial Department, and Mr. and Mrs. George Atkins, Department of Medical Illustrations, Ochsner Clinic, deserve special consideration. Doctor Hans Elias and Doctor Hans Popper provided the majority of illustrations in Chapter 3 and kindly permitted the use of the results of their classical investigations. Doctor Robert M. Kark and Doctor Erwin Kaplin rendered invaluable assistance in reappraising the clinical course my patients with hemochromatosis. A constant source of inspiration have been my professional associates and students, who were largely responsible for stimulating discussions on cirrhosis. The members of the American Association for the Study of Liver Diseases provided a valuable source of ideas and reports. During the years of preparation it was my wife who saw that the study was quiet and managed the home. She never made me feel that this preparation was unjustifiable. After her housework she voluntarily assumed the responsibility of arranging the bibliography and editing the manuscript. Her help was immeasurable. Both of us are grateful for the encouragement of our parents and the wonderful assistance of Charles C Thomas, my publisher, and his colleagues. Some of the investigations were sponsored by research grants awarded by the Committee on Research of the Council on Drugs of the American Medical Association, the Department of Health, Education and

Welfare, Public Health Service, National Institutes of Health, and the Lakeside Laboratories, Milwaukee, Wisconsin.

Many thanks are due my academic and clinical colleagues who unhesitantly offered their time and assistance during the long hours of preparing this manuscript. The author wishes to express his sincere appreciation to the authors, editors, and publishers of the various journals, and to those friends throughout the world, who sent specimens and illustrations for their permission to reproduce their material, published elsewhere. To all of these physicians, investigators, technicians and publishing personnel, I take this opportunity to express my gratitude for their contributions and co-operation.

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Chapter 1

INTRODUCTION

THE NEOPHYTE physician soon realizes that cirrhosis of the liver is a common disease observed in the outpatient clinics and wards of the hospital.[15] He probably had been taught, in most instances, that cirrhosis was cryptogenic and was recognized by certain characteristic pathological and clinical findings, was reflected in obscure abnormal hepatic functions, and was treated generally by supportive measures. Within the past two decades, however, diseases of the liver have attracted the attention of a large number of investigators, as disclosed in the majority of bibliographical references in this book. Interest in cirrhosis, relatively dormant for a long time, was revived by several accomplishments. These were principally: needle biopsy of the liver; etiology, epidemiology and sequelae of viral hepatitis; profile of "hepatic-function tests"; studies of the morphogenesis of hepatic injury in humans and experimental animals; dietotherapy; and the surgical treatment of portal hypertension. Needle biopsy has provided a fundamental method for a morphological classification of hepatic diseases and for better appraisal and application of "hepatic-function tests." In addition, significant progress has been made as the result of innumerable investigations on the biochemical and physiological aspects of the normal and diseased liver (Table I).

All of these studies have served to establish basic, but actually fragmentary, pathophysiological concepts for diagnosis and treatment of patients with cirrhosis. The functions of the liver are too numerous and its functional reserve and regenerative capacity so potentially marked during disease, that it is only when an hepatic lesion is in advanced stages that clinical manifestations appear. This usually depends on several factors, which modify and individualize the clinical picture, functions, morphology, sequelae and survival of patients with hepatic disease: the type and virulence of the etiological factor, the susceptibility of the

TABLE I

DEATH RATE PER 100,000 POPULATION FOR SELECTED CAUSES UNITED STATES

(Department of Health, Education and Welfare)

	1946	*1956*
1	Cardiovascular diseases—490.0	Cardiovascular diseases—501.5
2	Malignant neoplasms, including neoplasms of lymphatic and hematopoietic tissues—131.0	Malignant neoplasms including neoplasms of lymphatic and hematopoietic tissues—146.6
3	Accidents—66.3	Accidents—56.4
4	Other causes—52.7	Other causes—43.2
5	Diseases of early infancy—46.5	Diseases of early infancy—38.7
6	Influenza and pneumonia, except pneumonia of newborn—40.3	Influenza and pneumonia, except pneumonia of newborn—28.3
7	Tuberculosis—34.9	Diabetes mellitus—15.8
8	Chronic and unspecified nephritis and other renal sclerosis—20.0	Congenital malformations—12.7
9	Symptoms, senility and ill defined conditions—19.6	Symptoms, senility and ill defined conditions—11.7
10	Diabetes mellitus—14.1	Cirrhosis—10.7
11	Congenital malformations—12.4	
12	Suicide—11.6	
13	Hernia and intestinal obstruction—8.5	
14	Cirrhosis—7.8	

hepatic cell, the type, duration, persistence and localization of the injury, the quantity of normal hepatic cells surviving after hepatic injury, age, sex, heredity and constitution, the manner of repair, whether there has been complete healing, fibrosis, infiltration, biliary obstruction, atrophy, hypertrophy, necrosis, cirrhosis or neoplasm and the association with other diseases. That the liver generally enjoys a phenomenal resistance or response to diseases is reflected in the following manner. (a) the regenerative capacity of the hepatic cell as has been demonstrated by complete restoration after partial (70 per cent) hepatectomy,[37] (b) unique anatomic and physiological position of the liver, particularly in regard to its excessive size; (c) bifocal blood supply (nutrition via the portal vein and higher blood pressure and oxygen via hepatic artery), interference with which results in atrophy but not necessarily in death; (d) formation of regenerative hepatic nodules, intrahepatic portavenous anastomoses and extrahepatic porta-systemic anastomoses in cirrhosis; (e) biliary excretion, obstruction of which may eventually, but not immediately, provoke significant hepatocellular dysfunction; (f) venous

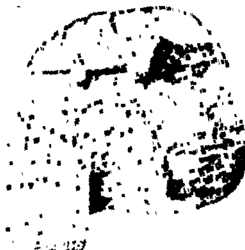


Fig. 1. Divination Liver. The Babylonians considered the liver the seat of the soul. About 2000 B.C. (British Museum Courtesy. Ralph H. Major—A History of Medicine. Vol. 1—Springfield, Thomas, 1954.)

outflow via the hepatic vein, obstruction of which may produce death, congestion, lymphatic engorgement, ascites and portal hypertension, (g) therapeutic benefit derived from glucose, (h) auxiliary functional reserves especially during disease, (i) function of detoxification, conjugation and excretion, (j) the integrated *enzymatic and metabolic activities between the hepatic cells* and other organs or their hormonal products, and (k) the hepatic tissues, (hepatic cells, bile ducts, reticuloendothelial or connective tissue framework, or blood vessels) may be selectively injured by a disease process.

Major diagnostic and therapeutic obstacles have been the lack of *specificity of the current "hepatic function tests"* and the difficulty in correlating the pathological, biochemical and clinical findings of cirrhosis. Whereas chronic inflammatory and degenerative diseases of other vital organs of the body have a fairly typical "textbook picture" and their diagnosis frequently is confirmed by abnormalities of tests measuring specific functions, diseases of the liver, in particular, cirrhosis, defy specific clinical

and functional measurement. The obscurity and plurality of functions of the normal liver, the integral relation of the liver with diseases of other organs, the different types of structural repair resulting from hepatic injuries and the unique regenerative capacity of the hepatic cell suggest that the liver is an unusually autonomous and complex organ

Malnutrition, especially diets deficient in protein, viral hepatitis, chemical poisons and obstructive lesions of the bile ducts are considered by most authorities as the most important, acceptable etiological factors of cirrhosis in humans. At the present time, however, these conditions do not explain, nor has any other conclusive evidence been advanced to explain, the pathogenesis of cirrhosis in patients with hemochromatosis, hepato-

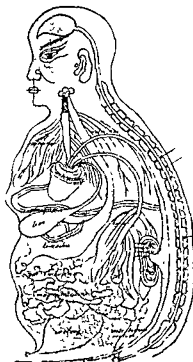


Fig 2 Chinese anatomical chart showing organs About 2000 B C The Chinese conceptions of the shape of the various organs and their topographical arrangement were rather vague (Courtesy, Clever—*Specimen Medicinae Sinicae* —Frankfurt, 1682)

lenticular degeneration, primary biliary cirrhosis or some types of cirrhosis present in infants and children. Etiologically, very little correlation can be demonstrated between cirrhosis in humans and nutritional and toxic cirrhosis in animals.

Actually, cirrhosis should be considered in two general aspects. First, it is a specific entity which includes several clinicopathological types, and second, in a broader sense, it is one of the findings complicating a general diagnosis of other diseases. The latter is exemplified by cirrhosis associated, for example, with hemochromatosis, hepatolenticular degeneration, chronic ulcerative colitis, parasitic infestations and thyrotoxicosis. Consideration of these distinctions and the obscure or apparently different etiological factors have contributed to the great difficulty in defining and classifying cirrhosis. The relation and influence of other organs or systems upon the liver, and the converse, suggests cirrhosis as a general rather than focal disease.

DEFINITION OF CIRRHOSIS

In order to organize a study of cirrhosis as well as possible at the present time, it is necessary, first, to define cirrhosis in a morphological manner. Some investigators have been cognizant of the inadequacy of the term cirrhosis and have discarded it in favor of architectural designations such as fibrosis, hardening, scarring, sclerosis, nodules and atrophy. The original term of "cirrhosis" was inadequate. Laennec, in 1826, first employed this term, deriving it from the Greek word "kirrhos," connoting tawny, because the regenerative nodules were "fawn or yellowish russet, bordering on the greenish." That this description was misleading is disclosed by the different descriptions and classifications of this condition. Despite the inadequacy of the term cirrhosis, it has descriptive implications and "has, by universal consent, become too firmly established to be displaced."[35] The term cirrhosis employed in this book is morphological and reflects the criteria proposed by Rössle in 1930 and de Josselin de Jong in 1931 as follows: (1) degeneration and necrosis of hepatic cells, (2) proliferation of connective tissue (stroma) and (3) (nodular) regeneration of hepatic cells.[13,17,46]

INDIVIDUAL VARIATIONS AFFECTING THE INCIDENCE AND TYPE OF CIRRHOSIS

A survey of cirrhosis in humans in one section of the country or world may have limited significance and may not be representative of this condition in other geographical areas. There are certain variables contributing to the difficulty of the interpretation, classification and discussion of cirrhosis.[51] These are age, sex, inheritance, race, nationality and occupation. For example, the author of a textbook on cirrhosis studying this condition in the United States should recognize that his observations and statistics may vary with those compiled from other sources throughout the world. The following examples illustrate this point of contention: (1) age—the predominence of infantile biliary cirrhosis in India and zooparasitic cirrhosis in children in the Orient, (2) sex—the greater incidence of cirrhosis in women residing on the continent and in tropical zones and also in women in the menarche and postmenopausal period, (3) inheritance—reports of congenital cirrhosis, familial hemochromatosis and hepatolenticular degeneration, (4) race—the reported frequency of cirrhosis in Orientals and African Negroes; (5) nationality—the increased incidence of cirrhosis among the inhabitants of India, South America and among the Irish and Italians and (6) occupation—cirrhosis occurring commonly among bartenders, farmers in the Orient, employees in chemical plants and salesmen. Other variables that may affect general reports, which should be considered by the reader, are the economic status of the patient, particularly with regard to malnutrition and alcoholism, the source of the patients, whether reported from data obtained in private practice or private or general hospitals; types of diagnostic methods employed, methods of treatment and the past occurrence of infectious hepatitis. Statistics, treatment and prognosis of cirrhosis reported from areas within and foreign to the United States should be guided by these divergencies.

IMPORTANT LANDMARKS IN THE HISTORY OF CIRRHOSIS

In order to appreciate the historical background of cirrhosis the student must not only review the general aspects of medical

history but the early descriptive studies of the normal liver To include all of the names of the students who have perpetuated the progress of the study of cirrhosis would be voluminous I have attempted briefly to categorize the history of cirrhosis into four eras. These must be reviewed by the reader as an adjunct



Fig 3. Statue thought to be that of Hippocrates (460–377 B C) Excavated on the Isle of Cos by Prof Luciano Laurenzi in 1929 School of Praxiteles, probable date, middle of fourth century B C (Photo Courtesy Ralph H Major)

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Pioneer medieval anatomist author of "Anatomia Hepatis" on which is based modern knowledge of the anatomy of the liver, gallbladder and bileducts

Fig 5a (Courtesy, G. D. Searle & Company.)

paracentesis. (350 B.C.) Diocles of Carystos described hepatic ascites; Erasistratos of Alexandria, father of physiology, described the hard liver and ascites. Roman Medicine: (A.D. 25-50) Celsus *de medicina* and hepatosplenomegaly, anasarca and paracentesis. (A.D. 100-200 [?]) Aretaios (Aretaeus) of Cappadocia works in clinical medicine including description of ascites and obstructive jaundice; (A.D. 40-90) Dioskorides *Materia Medica* including treatment of liver diseases. (A.D. 130-200) Galen classic indoc-

to the historical developments of the liver and its diseases (Figs 1-20).[22,26,27,31,32,33,34,35,39,41]

(1) *Ancient Conceptions of Cirrhosis.* (3500 B C) Babylonian devination and inspection of the liver; (3000 B C.) Egyptian, Chinese and Puruvian knowledge of the liver, jaundice, hepatitis, "cirrhosis" with ascites. Greek Medicine (570-489 B C) Pythagoras humoral theory;[3] (460-377 B C.) Hippocrates, father of medicine, description of disease in *corpus Hippocraticum* and



Fig 4 Antonio Benivieni (1443-1502). (Photo, courtesy Alinari)





Tabulae Hepar a Parenchymate
Suo Liberatum Exhibent
Francisci Glissonii, Anatomia Hepatis
Pub Joahnem Janssonium a Waesberge, 1665

Fig 5b (1597–1677) (Courtesy, G D. Searle & Company)

trinates of scientific medicine and described "cardiac disease with an excess of yellow-bile." Byzantine Medicine: (A.D. 525-605) Alexander of Tralles and (A.D 625-690) Paul of Aegina physical findings of hepatic-ascites and treatment of, by chologogues (biliary purgatives), dehydration, paracentesis Arabian Medicine (980-1037) Ibu Sina (Avicenna) wrote a classic medical book, *Canon,* and described obstructive and hemolytic jaundice; (1180-1250) Gilbertus Anglicus of the Salerno School discussion of jaundice in *Compendium Medicinae;* (1280-1361) John of Gaddesden wrote *The Rosa Anglica* and suggested salt-poor bread for dropsy; establishment of the renowned medieval medical universities in Europe

(2) *Renaissance of Anatomy, Scientific Medicine and Clinicopathological Studies of Cirrhosis:* (1443-1502) Benivieni published the first book on pathology; (1452-1519) Leonardo da Vinci, accurate anatomical drawing, (1514-1564) Vesalius, *De Humanis Corporis Fabrica,* classical description of human anatomy; (1520-1606) de Mercado authored a book on diseases of

et causis morborum and described hepatic disease. (1788) Andre described the regenerative nodules of cirrhosis.[8]

(5) *Era of Modern Medicine; Investigations of Cirrhosis* (1761-1823) Baillie, wrote *Morbid Anatomy of Some of the Most Important Parts of the Human Body*, and described cirrhosis as the common tubercle;[5] (1781-1826) Laennec described and named cirrhosis.[29] (1791-1874) Cruveilhier, original description of syndrome of caput medusae, venous hum and hepatic atrophy.[11] (1789-1858) Richard Bright studied hepatic diseases and "alcoholic" cirrhosis; (1793-1860) Addison described with Sir William Gull (1816-1890) chronic jaundice, vitiligoidia and xanthomatosis.[17] (1833) Kiernan, accurate description of hepatic lobule and circulation.[29] (1839) Power described esophageal



Fig 8 Matthew Baille (1761-1823)



Fig 7 Marcello Malpighi (1628–1694). From portrait in the Galeria Borghese, Rome

(1624-1689) Sydenham classic descriptions of clinical diseases; (1620-1695) Wepfer,[50] (1628-1694) Bidloo, histology of the liver; (1642-1700) John Browne, in 1685, described cirrhosis in an article "A Human Liver Appearing Glandulus to the Eye," in the *Transactions of the Royal Society*;[9] (1649-1713) Malpighi, hepatic histology;[38] (1682-1771) Morgagni wrote classic *De sedibus*

varices.[12] (1801-1867) Trousseau described hemochromatosis,[17] (1813-1878) Claude Bernard discovered hepatic glycogenesis; (1804-1878) Rokitansky wrote classic *Handbuch der Pathologischen Anatomie* and classified hepatic disease;[44] (1813-1819) Baumgarten described alcoholic fatty cirrhosis and Cruveilhier's syndrome; (1816-1898) West described cirrhosis in infants; (1819-1885) Frerichs described hepatic coma,[29] (1821-1902) Virchow, published the revolutionary treatise *Cellularpathologie;* (1822-1902) Kussmaul, first to perform esophagoscopy and gastroscopy; (1858-1931) Minkowski produced experimental fatty liver in pancreatectomized animals; (1825-1893) Charcot described secondary biliary cirrhosis;[12] (1833-1910) von Reckling-



Fig 11 Richard Bright (1789–1858) From portrait by T. R Say



Fig 9 René Théophile Hyacinthe Laennec (1781–1826) (Photo, courtesy, Ralph H Major)



Fig 10 Giovanni Battista Morgagni (1682–1771) Engraving by Angela Kauffman (Courtesy, University of Kansas Collection)



Fig 13 Thomas Addison (1793–1860) Frontispiece of *A Collection of the Published Writings of Thomas Addison*—London, 1868



Fig 14 Carl Rokitansky (1804–1878) (Photo, courtesy, Ralph H Major—A History of Medicine—Springfield Thomas, 1954)



Fig 12 Jean Cruveilhier (1791-1874) From an engraving by Lasnier (Courtesy, University of Kansas Collection.)

hausen, named hemochromatosis; (1854) Jones, H., described biliary cirrhosis; (1857) Budd wrote a textbook on diseases of the liver,[11] (1865) Paul described thyrotoxicosis with cirrhosis, (1873) Legg, described secondary biliary cirrhosis; (1876) Hanot described hypertrophic (primary) biliary cirrhosis;[23] (1887) Howard, R. P., described cirrhosis in infants and children; (1898) Banti, syndrome of splenic anemia and cirrhosis;[5] (1895) Marchand described hepatic course nodular hyperplasia,[39] (1896)



Fig. 16 Claude Bernard (1813–1878). Statue in front of Collège de France, Paris (Photo, courtesy, Major, Ralph H.)

has increased the applications of clinical and pathological studies of cirrhosis to investigations dealing with hepatic functions, intermediary metabolism and medical and surgical treatment. The men responsible for these accomplishments are alluded to in the text. They have revolutionized the general concept of cirrhosis, and, in fact, are responsible for originating hepatology. That this



Fig 15 Armand Trousseau (1801–1867) Photo by Trinquart in the *Académie de Médecine*, Paris (Courtesy, University of Kansas Collection)

Van Henkelom emphasized hepatic regeneration,[40] (1822-1865) Baerensprung described syphilitic cirrhosis (gumma); (1845-1915) Gowers first described "tetanoid chorea" case of hepatolenticular degeneration,[23] (1849-1920) Osler wrote *Principle and Practice of Medicine*, early pioneers of protein metabolism (1802-1880) Neulder, (1803-1873) von Liebeg, (1852-1919) Fischer, (1853-1927) Kossel; (1854-1932) Rubner, (1856-1913) Chittenden; (1895) Lucatello introduced needle biopsy of the liver; (1862-1914) Rolleston and McNee, outstanding textbook on *Disease of The Liver, Gallbladder and Bile Ducts.*[45]

(4) *Era of Scientific Medicine and Treatment, Etiology, Pathogenesis, Classification and Medical and Surgical Treatment of Cirrhosis.* The Twentieth Century characterizes outstanding investigations of the etiological, pathogenetic, physiological, biochemical and therapeutic manifestations of cirrhosis This era

function profiles and needle biopsy of the liver should be employed with greater frequency in these patients in order to determine the morphogenic precursors of cirrhosis. It is necessary to determine the presence of anicteric hepatitis, which conceivably may account for many cases of cirrhosis. Additional information on the epidemiology and virology of the viruses IH and SH is necessary in order to discover an effective virucidal drug.[13,17,40]

Progress is also necessary in the investigation of the biochemical and physiological functions of the normal and abnormal



Fig. 18. *William Withey Gull* (1816–1890). (From *Published Writings of William Withey Gull*—London, 1896.)

science already appears overdeveloped is suggested by the apparent subspecialized interests in the study of the liver and its diseases. In 1950 the American Association for the Study of Liver Diseases was organized by Hans Popper and their meetings and publications emphasize the remarkable proliferative efforts in investigation and the accomplishments of many men, particularly since 1930.

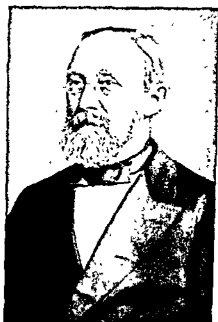


Fig 17 Rudolf Virchow (1821–1902) (Photograph, courtesy, University of Kansas Collection)

THE FUTURE OF CIRRHOSIS

The investigation of cirrhosis in the future must be directed toward the solution of two main problems, namely those concerned with preventative medicine and biophysiology of the liver [illegible]

with acute febrile, "flu-like," or jaundiced conditions [illegible] Until this information is available, it would seem that hepatic-

function profiles and needle biopsy of the liver should be employed with greater frequency in these patients in order to determine the morphogenic precursors of cirrhosis. It is necessary to determine the presence of anicteric hepatitis, which conceivably may account for many cases of cirrhosis. Additional information on the epidemiology and virology of the viruses IH and SH is necessary in order to discover an effective virucidal drug.[13,17,49]

Progress is also necessary in the investigation of the biochemical and physiological functions of the normal and abnormal



Fig. 18. William Withey Gull (1816–1890). (From *Published Writings of William Withey Gull*—London, 1896.)

liver in order to develop more sensitive and specific hepatic function tests and to clarify the pathogenesis of hepatic insufficiency and coma, ascites and portal hypertension The fact that these advances are being effected is witnessed by the wealth of investigative data appearing in the monthly medical journals[5,6]



Fig 19 Jean-Martin Charcot (1825–1893). (Photo, courtesy, Ralph H Major —A History of Medicine—Springfield, Thomas, 1954)

Studies of the significance of the biogenetic and constitutional factors in cirrhosis seem to be indicated.[31] Early management of the emotional and dietary problems of the chronic alcoholic are necessary in order to arrest the development of cirrhosis in these patients. Benefit may be derived from the co-operative efforts of the alcoholic clinic, the psychiatrist and hepatologist. The possible pathogenetic role of the liver should be studied in patients and their families who have so-called metabolic cirrhosis such



Fig. 20. S. A. Kinnier Wilson (1878–1937)

as hemochromatosis, hepatolenticular degeneration, congenital cirrhosis and in galactosemia Finally, it has been observed that only a few outstanding and selected medical organizations in the world devote much of their scientific sessions to the study of diseases of the liver. It is necessary that the pioneer interest in the liver and its diseases kindled by the American Association for the Study of Liver Diseases be extended throughout the world.[42] Students of the liver may some day meet their colleagues from other parts of the globe at a yearly world conference on Liver Diseases Such an assembly as witnessed by the World Congress of Gastroenterology in Washington, D C. in 1958[32] will serve as an international medium for the better understanding of the problems of the liver.

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Chapter 2

EXPERIMENTAL CIRRHOSIS

INTRODUCTION

An abundant amount of investigative material has been published since 1930 on the experimental production of hepatic damage in animals. Fatty liver, hepatic necrosis, cirrhosis and primary neoplasms of the liver have been described in various experimental animals as the result particularly of dietary deficiencies and the exposure of chemicals toxins. This, of course, interests the clinician because he is unable usually to explain satisfactorily the exact etiological factor and the pathogenesis of cirrhosis. However, there are certain clinical applications and limitations derived from these investigations of hepatic disease produced experimentally in various animals. Too often the role of a particular dietary factor responsible for hepatic lesions in animals is difficult to interpret in light of nutritional diseases of the liver observed in humans. Racial or constitutional factors, heredity, and dietary habits of humans are but a few qualifications to be considered when one attempts to correlate hepatic disease in animals and humans. Elias and Popper found differences between man and rat in the distribution of the branches of the portal vein and hepatic vein and lymphatics.[49] They caution against any conclusions drawn from experimental animals as to the morphogenesis of cirrhosis when applied to the human liver. Biological variabilities and predisposition to diseases such as cirrhosis occurring in humans have been analyzed by Williams who has promulgated the genetotrophic concept of disease.[191]

The precise pathogenetic role of dietary factors which explain the production and arrest of hepatic necrosis, fatty liver and cirrhosis of the portal or postnecrotic variety in animals does not blend with the etiological and pathogenetic concepts of clinical hepatic disease. The results observed in experimental animals, for example, the production and correction of nutritional hepatic damage dependent on the amount of methionine or choline in

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Lillie in 1912 were the first investigators to differentiate dietary cirrhosis and dietary hepatic necrosis as separate etiological and morphological entities in animals[25,26] They stated that "choline prevents cirrhosis, cystine prevents the hemorrhagic necrosis, and methionine prevents both the cirrhosis and hemorrhagic necrosis" and concluded as others have done subsequently that these two deficiency syndromes were distinct and unrelated. In 1935 Weichselbaum produced "hemorrhages throughout the liver" and jaundice in animals administered a diet deficient in cystine or methionine[19] This lesion was identified subsequently the following year by György and Goldblatt, and du Vigneaud and his associates as hepatic necrosis[illegible] In 1943 Hock and Fink produced hepatic necrosis in rats administered yeast as the sole source of protein, and the inclusion of cystine in the yeast diet prevented this lesion[99] These early works in the experimental production of dietary hepatic injury were followed by the classical investigations of Himsworth and Glynn in 1944. They were able to produce two basic types of dietary liver disease which may progress to gross cirrhosis, namely, acute massive necrosis and fat infiltrated diffuse hepatic fibrosis (Table I).[100-102]

THE LIPOTROPIC FACTORS

Certain dietary lipotropic factors such as choline, methionine, betaine, vitamin B_{12} and inositol have been found to retard fatty livers and cirrhosis in rats A fatty liver has been considered a morphological precursor resembling the portal type in experimental animals In man, on the other hand, the relationship of lipotropic agents in the evolution of cirrhosis has been discredited In fact, it has been argued that fatty infiltration of the liver, which is present in alcoholic patients suffering from malnutrition, does not lead to cirrhosis and that hepatocellular necrosis and alcoholic hyaline bodies are more important histological findings A review of the lipotropic agents is necessary in order to understand clearly the pathogenesis of experimental cirrhosis.

The experimental production of diabetes mellitus and fatty infiltration of the liver in depancreatized dogs by von Mering and Minkowski in 1889 was one of the first efforts in the investigation of hepatic injury[illegible] In 1924 Allan and his co-workers



FIG 1 Dietary necrotic liver degeneration (Courtesy, Schwarz, K — Proc Soc Exper Biol & Med — 1951)

the diet, do not explain but actually conflict with investigative data on the role of these lipotropes in nutritional hepatic disease in humans This is observed despite similarity of the pathological conditions such as fatty liver and cirrhosis Himsworth has stated that the results of experimental dietary injury to the liver have led to "most discordant results" and "it is no exaggeration to say at one time or another every dietary component save carbohydrates has been indicted" in the pathogenesis of hepatic disease in animals [99] Despite the fact that there is little relationship between these experimental findings and the problem of clinical nutritional disease including cirrhosis, it is worthwhile to review this complex problem Essentially, two specific hepatic lesions produced experimentally in animals, namely, the fatty liver and hepatic necrosis, will be considered as morphologic precursors to the formation of cirrhosis and hepatic tumors. Daft, Sebrell, and

protein, in general, depends on choline or methyl group precursors was concluded by Best, Huntsman and Ridout in 1935.[11] Eventually, it was demonstrated that prolonged choline deficiency in animals caused cirrhosis and hepatoma.[92]

In 1937 Tucker and Eckstein discovered that methionine, an essential amino acid containing sulfur, had a lipotropic effect.[154] When methionine supplies its methyl radical for the formation and activation of choline, it is converted to homocysteine. It has been found to arrest the development of fatty livers produced by diets deficient in protein. Choline facilitates the mobilization and transport of fat from the liver by combining with fatty acids to form phospholipids. It has been found that lipotropic action of radioactive choline was dependent upon the hepatic utilization of phospholipids.[193]

The importance of methionine was also demonstrated by Himsworth and Glynn in 1944 who produced hepatic necrosis



Fig. 2. (*Left*) Beginning "scarring" of liver from animal on liver necrosis producing diets. (Courtesy, Schwarz, K.—Proc. Soc. Exp. Biol. & Med.—77: 818, 1951.) (*Right*) Control.

TABLE I
Experimental Nutritional Hepatic Disease

1 *Fatty Liver*	Diffuse Hepatic Fibrosis Portal Cirrhosis Primary Carcinoma
1 Deficiency of lipotropic agents (choline, methionine, betaine inositol vitamin B_{12}, folic acid, citrovorum factor) 2 Broad spectrum antibiotics 3 Dietary cystine 4 Diets low in protein or high in fat 5 Alcohol in conjunction with protein deficient diets 6 Ethionine (antagonist of methionine) 7 Pancreatectomy (lecithin deficiency)	
2 *Hepatic Necrosis*	Postnecrotic Scarring Postnecrotic Cirrhosis Primary Carcinoma
1 *Deficiency of cystine, methionine, alpha-tocopherol, and factor 3* 2 Protein deficient diets (yeast) 3 Ethionine (antagonist of methionine) 4 Bromobenzene (antagonist of cystine)	

demonstrated that hepatic failure and fatty livers developed in depancreatized dogs maintained alive by insulin, and that this lesion could be ameliorated by feedings of raw pancreas[1] Hershey in 1930 and Hershey and Soskin in 1931 working in C H Best's laboratory in Toronto discovered that fatty infiltration of the liver was prevented in these animals by the administration of lecithin[97,98] In 1932 Best, Hershey and Huntsman also produced fatty livers in rats fed a low-protein, high-fat diet, and noted that this lesion could be prevented or reversed by the addition of dietary lecithin.[8] These investigators subsequently identified choline as the active ingredient of lecithin[7,5-14] The following year choline was found effective in the treatment and prevention of depancreatized, insulin-treated dogs[8,141 142 156] In 1936 Dragstedt and his co-workers reported that fatty livers in insulin-treated depancreatized dogs were due to a deficiency of a specific pancreatic hormone, lipocaic.[43-45 50] Its lipotropic property is now considered to be due to or identical with choline. Best coined the term, lipotropic, to describe any dietary factor which prevents or cures deposits of fat in the liver. Subsequently, betaine, methionine and casein, a protein found to contain choline, were found to have lipotropic properties. That the lipotropic property of

found to produce fatty livers in rats. This can be prevented by the use of methionine.[155] Hall and Drill in 1918 discovered that liver extract had a lipotropic activity in rats fed a high-fat diet, probably related to choline deficiency.[83] A year later Schaefer and co-workers found that vitamin B_{12} had a sparing action in the choline requirement of rats and chicks.[144,165,142] This vitamin was noted to be necessary for the liver to convert betaine and homocystine to methionine or choline and homocystine to methionine.[44,65] Vitamin B_{12} or folic acid were found to be lipotropic factors in rats fed diets low in choline.[85,95,152]

There may be other factors present in addition to lipotropes or diets which prevent fatty livers in experimental animals. Farber found young male animals the group most susceptible to experimental dietary hepatic injury.[59,134,160] In general, the dietary factors, choline, betaine, vitamin B_{12}, folic acid and the citrovorum factor protect against the production of fatty cirrhosis and enhance the development of hepatic necrosis in experimental animals. Methionine, while protective against fatty livers and cirrhosis, is also slightly protective in dietary hepatic necrosis, since it is partly metabolized to cystine.[122,123,152] Bromobenzene, an antagonist of cystine, aids in producing hepatic necrosis.[113] Cystine, protein, vitamin E, Factor 3 (the protective factor in casein) and mucin have been found to retard hepatic necrosis and enhance the production of fatty livers and cirrhosis.[62,64,65,99,104,166-169] Daft and co-workers in 1911 also found that cystine protected against the production of cirrhosis experimentally in animals subsisting on a protein deficient diet.[35,36,181] Diets deficient in alpha-tocopherol and protein have been demonstrated to induce hepatic necrosis in experiment animals.[104,166]

There are other amino acids including those containing sulfur that influence the production of fatty livers and cirrhosis in experimental animals. It has been demonstrated that threonine, glycine, leucine, l–tryptophane, lycine, 5 per cent casein, and gelatin are lipotropic agents.[41,103] Himsworth and Glynn produced two main types of experimental dietary hepatic injury.[99] One type, massive hepatic necrosis produced by protein-deficient *diets, could* be prevented by methionine, cystine and alpha



FIG 3 Cirrhotic Liver of Rat (Courtesy, Schwarz, K)

in rats by administering a diet containing daily increments of 200 mg. of casein or yeast, when methionine was added to these diets hepatic necrosis was prevented[99,100] They disclosed that "postnecrotic scarring" (postnecrotic cirrhosis) also eventually could be produced experimentally in animals fed diets deficient in methionine but adequate in the content of choline. A cirrhosis-protecting factor independent of the lipotropic factor has been postulated for methionine. Other lipotropic agents have been identified. Gavin and McHenry in 1941 found that inositol was a lipotropic factor in the prevention of a biotin-fatty liver.[59] Ethionine, the metabolic antagonist of methionine, has been

sisting on a high-fat diet.[21,24] They also demonstrated the resolution of fat as cirrhosis progressed. Connor's important study of the transition from a fatty liver to cirrhosis in humans parallels this animal study.[31,32] Fatty livers have also been produced in experimental animals administered alcohol.[11,12,32] Choline has also been found to prevent and repair fatty liver and cirrhosis on high fat, low-protein diets. Fatty livers as the result of alcohol or fat diets not only have been considered to be due to protein and vitamin B-complex deficiency but to functional overload by excessive ingestion of food.[42,120,121,126] The production of fatty livers and cirrhosis by high fat, low protein diets has been found to increase the susceptibility of the liver to hepatotoxic agents.[11,13,15-17,54,178-180] The chemical nature of fat has been determined to be important in producing fatty livers experimentally. Spellberg found that butter fat produced marked fatty infiltration of the liver in guinea pigs, and hydrogenated vegetable oil, only minimal changes.[180] Not only the administration of diets with increased fat, unsaturated fatty acid content, or castor oil, but also those deficient in choline and possibly alpha tocopherol produce an acid-fast, brownish, fat staining pigment, called ceroid, in areas of hepatic fibrosis.[69,70-75] The significance of ceroid is obscure and it has been discovered rarely in cirrhosis in humans.

A study of the histological sequence of events in the production of experimental fatty livers and cirrhosis was begun by Hartroft and colleagues in 1950 in the Banting and Best Department of Medical Research at the University of Toronto (Figs. 4-11).[39,94] Several hours after rats had been fed choline-deficient diets, intracellular fat accumulated in the hepatic cells particularly in the centrilobular and nonportal regions of the liver. This phase, intracellular lipohepatosis, is followed by extracellular lipohepatosis, i.e., the formation of fatty cysts as the results of released intrahepatic fat. Rupture of the fatty cysts then occurs with the formation of trabecular fibrosis, the early stage of cirrhosis. The trabeculae are nonportal in distribution and subsequently, fibrosis develops in the portal triads replacing parenchyma. The parenchyma adjacent to the conducting veins is supplied by sinusoids. The sinusoids, in most instances, receive

tocopherol and, depending upon the survival of the animal, could progress to postnecrotic scarring While this appears grossly as cirrhosis, Hoffbauer and Wittenburg do not recognize this as cirrhosis as in the case of fatty liver-cirrhosis metamorphosis, because of the absence of regenerative nodules and extensive fibrosis [102a] The second lesion described by Himsworth and Glynn is diffuse hepatic fibrosis produced by a high-fat, moderate-protein diet (Figs 1-3). The progression of a fatty liver to a fibrotic liver and cirrhosis occurs and is attributed to deficient lipotropic agents containing labile methyl groups/

THE ROLE OF PROTEIN, CARBOHYDRATE AND FAT IN EXPERIMENTAL CIRRHOSIS

Attention has been called to the production of fatty liver, necrosis and cirrhosis due to different types of diets deficient in various lipotropic factors and essential amino acids. The addition of choline, the sulfur-containing amino acids, methionine, in particular, and increased amounts of casein to low-protein diets have been shown experimentally to prevent the development of these hepatic lesions The arrest of fatty infiltration, and the regeneration of hepatic cells without any resolution of fibrosis can be demonstrated histologically as the result of these protective diets/Protein and the lipotropic agents have been found effective in retarding experimental cirrhosis from carbon tetrachloride/[12,18,19,159,198] Patek, Plough and Bevens studied the reparative effect of 30 per cent casein fed to rats with nutritional cirrhosis [152] They noted that this diet was more effective than a 4 per cent casein diet with supplementary choline and methionine in inhibiting experimental cirrhosis The importance of dietary protein and content of hepatic protein has been stressed in repair of hepatic injury, especially with regard to hepatocellular regeneration [67,147,165]

/Dietary fat also plays an important role in producing hepatic injury. Obesity as the result of diets high in fat has been demonstrated to be associated with impaired hepatic function and fatty livers in both humans and experimental animals [20-23,47,133,194] Chaikoff and others in 1940 and 1943 have shown that fatty infiltration of liver is converted to a non-fatty cirrhosis in dogs sub-

sisting on a high fat diet.[21,23] They also demonstrated the resolution of fat as cirrhosis progressed. Connor's important study of the transition from a fatty liver to cirrhosis in humans parallels this animal study.[31,32] Fatty livers have also been produced in experimental animals administered alcohol.[11,17,22] Choline has also been found to prevent and repair fatty liver and cirrhosis on high fat, low-protein diets. Fatty livers as the result of alcohol or fat diets not only have been considered to be due to protein and vitamin B-complex deficiency but to functional overload by excessive ingestion of food.[42,120,121,126] The production of fatty livers and cirrhosis by high-fat, low-protein diets has been found to increase the susceptibility of the liver to hepatotoxic agents.[31,32,15-17,46,115,150] The chemical nature of fat has been determined to be important in producing fatty livers experimentally. Spellberg found that butter fat produced marked fatty infiltration of the liver in guinea pigs, and hydrogenated vegetable oil, only minimal changes.[150] Not only the administration of diets with increased fat, unsaturated fatty acid content, or castor oil, but also those deficient in choline and possibly alpha tocopherol produce an acid fast, brownish, fat-staining pigment called ceroid, in areas of hepatic fibrosis.[97,10-13] The significance of ceroid is obscure and it has been discovered rarely in cirrhosis in humans.

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THE ROLE OF PROTEIN, CARBOHYDRATE AND FAT IN EXPERIMENTAL CIRRHOSIS

Attention has been called to the production of fatty liver, necrosis and cirrhosis due to different types of diets deficient in various lipotropic factors and essential amino acids. The addition of choline, the sulfur-containing amino acids, methionine, in particular, and increased amounts of casein to low-protein diets have been shown experimentally to prevent the development of these hepatic lesions The arrest of fatty infiltration, and the regeneration of hepatic cells without any resolution of fibrosis can be demonstrated histologically as the result of these protective diets. Protein and the lipotropic agents have been found effective in retarding experimental cirrhosis from carbon tetrachloride,[12,18, 19 169 199] Patek, Plough and Bevens studied the reparative effect of 30 per cent casein fed to rats with nutritional cirrhosis [152] They noted that this diet was more effective than a 4 per cent casein diet with supplementary choline and methionine in inhibiting *experimental cirrhosis The importance of dietary protein and* content of hepatic protein has been stressed in repair of hepatic injury, especially with regard to hepatocellular regeneration,[67 147 155]

Dietary fat also plays an important role in producing hepatic injury Obesity as the result of diets high in fat has been demonstrated to be associated with impaired hepatic function and fatty livers in both humans and experimental animals,[20-24,47,133 194] Chaikoff and others in 1910 and 1913 have shown that fatty infiltration of liver is converted to a non-fatty cirrhosis in dogs sub-

sisting on a high fat diet [21,24] They also demonstrated the resolution of fat as cirrhosis progressed. Connor's important study of the transition from a fatty liver to cirrhosis in humans parallels this animal study.[31,32] Fatty livers have also been produced in experimental animals administered alcohol [11,12,32] Choline has also been found to prevent and repair fatty liver and cirrhosis on high fat, low-protein diets Fatty livers as the result of alcohol or fat diets not only have been considered to be due to protein and vitamin B-complex deficiency but to functional overload by excessive ingestion of food [42,120,121,126] The production of fatty livers and cirrhosis by high-fat, low protein diets has been found to increase the susceptibility of the liver to hepatotoxic agents [11,13,15-17,64,175-180] The chemical nature of fat has been determined to be important in producing fatty livers experimentally Spellberg found that butter fat produced marked fatty infiltration of the liver in guinea pigs, and hydrogenated vegetable oil, only minimal changes [180] Not only the administration of diets with increased fat, unsaturated fatty acid content, or castor oil, but also those deficient in choline and possibly alpha tocopherol produce an acid fast, brownish, fat staining pigment, called ceroid, in areas of hepatic fibrosis [45,70-73] The significance of ceroid is obscure and it has been discovered rarely in cirrhosis in humans

A study of the histological sequence of events in the production of experimental fatty livers and cirrhosis was begun by Hartroft and colleagues in 1950 in the Banting and Best Department of Medical Research at the University of Toronto (Figs 4-11) [82,84] Several hours after rats had been fed choline-deficient diets, intracellular fat accumulated in the hepatic cells particularly in the centrilobular and nonportal regions of the liver This phase, intracellular lipohepatosis, is followed by extracellular lipohepatosis, i e., the formation of fatty cysts as the results of released intrahepatic fat Rupture of the fatty cysts then occurs with the formation of trabecular fibrosis, the early stage of cirrhosis The trabeculae are nonportal in distribution and, subsequently, fibrosis develops in the portal triads replacing parenchyma The parenchyma adjacent to the conducting veins is supplied by sinusoids. The *sinusoids, in most instances,* receive

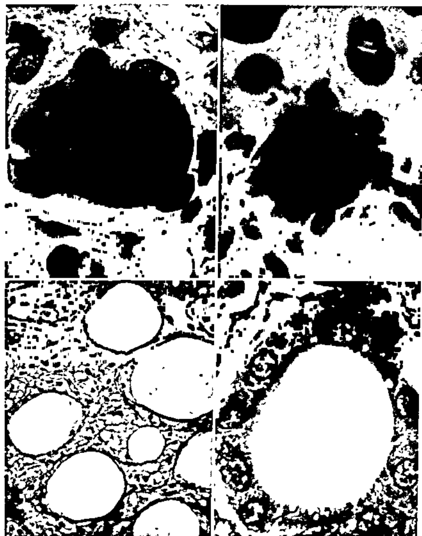


Fig 4 Frozen section of liver of an alcoholic patient coming to autopsy, Oil Red O and hematoxylin A fatty cyst is shown filled with lipid (black in photo) and surrounded by the nuclei of six hepatic cells (H & E, x 800). (Courtesy, Hartroft, W. Stanley, St Louis.)

Fig. 5 Frozen section, stained with Oil Red O, of the liver of a rat fed a choline-deficient diet for three months The fatty cyst is shrinking and losing its contents, as indicated by the fact that the nuclei in its wall now lie much closer together (H & E, x 800). (Courtesy, Hartroft, W. Stanley, St Louis)

their blood via others which communicate with terminal venules, which, in turn, distribute blood to the hepatic parenchyma. Rappaport and his co-workers have described the portal venules lying centrally in the structural unit of hepatic tissue as the hepatic acinus[137] Four or five months later mitotic figures appear in the parenchyma areas surrounding the terminal portal venule. Proliferation of these areas results in nodular regeneration, a striking gross feature of cirrhosis. Their growth compresses the surrounding fibrous trabeculae. Histological evidence of neoplasm may be observed eventually in the periphery of the regenerative nodule as Copeland and Salmon first described[33] Leakage of fat from cysts into the vascular system may occur and results in intermittent or persistent episodes of fat emboli being carried to the heart, kidneys and lungs and other organs. Hartroft has reported arteriosclerosis in the aorta, carotid and coronary arteries in choline-deficient rats which may be the result of fat emboli He considers the fatty cysts as the cytometaplastic links between lipohepatosis and cirrhosis and has observed them in cases of cirrhosis in humans at necropsy. Hartroft and Sellers have also disclosed mobilization of these fatty cysts by choline therapy[84] Fatty cysts have been described in man with dietary deficiency, alcoholism, obesity, kwashiorkor, and cirrhosis, but their significance in the production of human cirrhosis has been questioned[42,115,141] Some observers have felt that necrosis is a more important cirrhotogenic lesion than the presence of fat in the liver. Dubin has studied extensive serial biopsy material of fatty livers in humans and found that necrosis rather than fatty infiltration leads to cirrhosis[46]

FIG 6 Paraffin section of the liver of a rat fed a choline-deficient diet for three months Fatty cysts in the process of shrinking and atrophy are being replaced and surrounded by condensed reticulin (H & E, x 400). (Courtesy, Hartroft, W Stanley, St. Louis.)

FIG 7. A large fatty cyst in the liver of an alcoholic patient coming to autopsy Paraffin section stained with hematoxylin and eosin The wall of the cyst is clearly formed of at least nine liver cells (H & E, x 800) (Courtesy, Hartroft, W Stanley, St Louis)

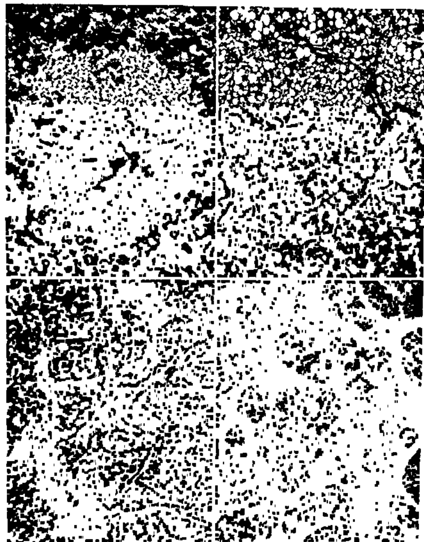


FIG 8. Fatty cysts in the liver of a choline-deficient rat from annular patterns linking central veins to adjacent central veins, thus foreshadowing the trabecular pattern of the fibrosis to follow The black area in the center represents a small portal triad Frozen section stained with Oil Red O (X200) (Courtesy, *Hartroft, W Stanley, St Louis*)

FIG 9 Paraffin section of the liver of a rat fed a choline-deficient diet for approximately twelve weeks The fibrous tissue (grey) forms an annular

Carbohydrates have been considered to possess a protective factor in human hepatic injury due to their protein-sparing action, their roles in the formation of hepatic glycogen, reduction of hepatic fat, and protection of a necrotic liver from the lethal effects of protein. The classic experiment of Mann demonstrated reversal of hypoglycemia in hepatectomized animals.[87, 129] Experimentally, diets high in carbohydrate have been found to protect the liver against various hepatotoxic agents. Generally, under experimental conditions, protein and the lipotropes have been found to be protective in fatty livers and cirrhosis, while carbohydrates, on the other hand, exert a greater protective action in extensive hepatic necrosis.

MISCELLANEOUS FACTORS PRODUCING DIETARY HEPATIC INJURY

The role of *intestinal bacteria in the production of fatty livers or hepatic necrosis* has been studied by several investigators. Sterilization of the intestinal tract in rats, by the administration of intestinal antibiotics, has been demonstrated to retard hepatic necrosis, in particular, and, also, dietary fatty liver and cirrhosis.[80, 81, 117, 150, 153, 154, 193] Broad spectrum antibiotics were found to exert a lipotropic action when fed to rats administered a diet low in protein and choline and high in fat content, and also inhibited

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pattern surrounding the portal triad in the center of the photomicrograph and mimicks that of the fatty cyst shown at an earlier stage in Figure 5. Connective tissue stain (approximately X200). (Courtesy, Hartroft, W. Stanley, St. Louis.)

FIG. 10. The illustration depicts a later stage than that of Figure 6, in which the fibrous tissue (grey) has now extended from central to portal areas forming a pattern somewhat like the spokes of a wheel. The portal area lies in the center. Connective tissue stain (X200). (Courtesy, Hartroft, W. Stanley, St. Louis.)

FIG. 11. Frozen section of the liver of a rat fed a choline-deficient diet for seven *months*. The cirrhosis is now fully advanced. Fibrous tissue bands have split up the parenchyma into many small units, as presaged in Figure 7. Some of these units have now undergone regeneration bringing about a variation in size. Note that some of the parenchymal nodules have several portal and central veins. Frozen section stained with Oil Red O (X100). (Courtesy, Hartroft, W. Stanley, St. Louis.)

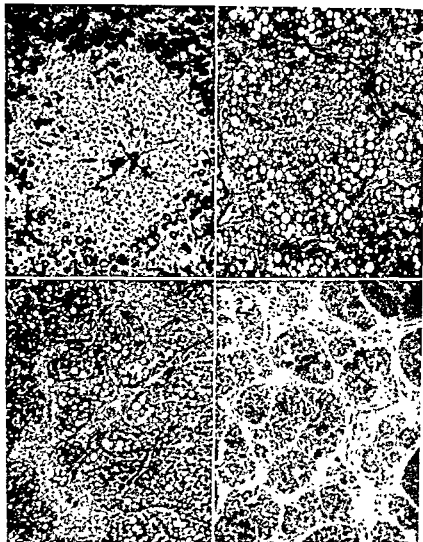


FIG 8 Fatty cysts in the liver of a choline-deficient rat from annular patterns linking central veins to adjacent central veins, thus foreshadowing the trabecular pattern of the fibrosis to follow. The black area in the center represents a small portal triad Frozen section stained with Oil Red O (X200) (Courtesy, Hartroft, W. Stanley, St Louis)

FIG 9. Paraffin section of the liver of a rat fed a choline-deficient diet for approximately twelve weeks The fibrous tissue (grey) forms an annular

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death, complete morphological recovery or cirrhosis eventuates in experimental animals exposed to a chemical depends on the dose, route of administration, repeated exposure, chemical composition, and the regenerative capacity of the liver. Carbon tetrachloride, benzene, lead, pyridine, ethyl urethane, phosphorus, and arsenic are some lethal hepatocellular agents which may induce experimental cirrhosis. Cincophen, and as alluded to, ethyl alcohol have been considered by some investigators as cirrhotogenic. Lethal doses of these hepatotoxic agents act directly on the hepatic cell and produce massive necrosis of the liver, whereas repeated exposure to sublethal doses under certain circumstances causes cirrhosis. Dietary conditions have been found to influence the susceptibility of the experimental animals exposed to hepatotoxic agents. A high-fat diet, low-protein diet, high-carbohydrate diet, vitamins E and B_{12}, methionine, cystine or choline, and antibiotics, respectively, afford protection to toxic hepatic injury. The preventative action of sulphur-containing amino acids in toxic hepatic damage due to cholorоform, for example, may be explained by preservation of the sulfhydryl enzymatic system or methylation. Consequently, it has been shown that two specific lesions, namely, fatty liver and hepatic necrosis, can be produced experimentally in animals by various diets and toxic agents. Fatty livers may progress to hepatic fibrosis or a cirrhosis resembling the portal variety as observed in humans. Hepatic necrosis, on the other hand, may heal by postnecrotic scarring or cirrhosis, which grossly resembles a postnecrotic variety. Both of these types of experimental cirrhosis may degenerate to hepatic tumors.

ROLE OF HEPATIC CIRCULATION IN EXPERIMENTAL CIRRHOSIS

An important vascular factor in cirrhosis is the "stream line phenomenon" of the portal vein in which the current of blood flowing from the splenic vein passes to the left lobe of the liver and that from the intestines to the right lobe via the superior mesenteric vein. Glenard first suggested that divisions of the liver obtain blood from various regions of the gastrointestinal tract, and Serege, in 1902, postulated that the portal vein had separate currents of blood.[129,170] Copher and Dick in 1928 confirmed the

hepatic necrosis in rats fed a necrogenic diet. Rats raised in a germ-free atmosphere did not develop hepatic necrosis even when fed a necrogenic diet. Sterilization of the intestinal tract has also been found to decrease the coliform flora and increase the number of Bacillus megatherium, a bacteria productive of large quantities of vitamin B_{12}, itself a lipotropic agent.[110] It is noteworthy that de la Huerga and Popper considered that intestinal bacteria converted choline to trimethylamine oxide.[105] Experimental animals were found to have elevated levels in the serum cholesterol and phospholipid and decreased levels of serum alkaline phosphatase On the other hand, the administration of broad-spectrum antibiotics has led to fatty infiltration of the liver in experimental animals, similar to the manner in which it occurs in humans[117, 161,193] Kaplan also has demonstrated that broad-spectrum antibiotics possess a lipotropic property when administered to dogs with ligated pancreatic ducts.[109-112] Depancreatized dogs and rats, or those in which the pancreatic ducts were ligated, and complemented with adequate insulin, developed fatty livers and had reduced levels of blood lipids and serum hyperphosphatemia.[52]

It has also been noted that certain environmental conditions, sex, age and type of experimental animal affected dietary hepatic injury Experimental production of fatty livers in animals also has been induced by nutritional obesity, by the administration of adrenal steroids, goitrogens or anterior pituitary extract, and by hypophysectomy, thyroidectomy or oophorectomy[3 23-27 51 53-56 60 73,76-78 82 84 118 119 125 126 145 171-174 180 191]

EXPERIMENTAL TOXIC PRODUCTION OF CIRRHOSIS

There are several hepatotoxins capable of producing experimental hepatic damage such as fatty infiltration, hepatic necrosis, fibrosis, cirrhosis and hepatic neoplasm For a comprehensive list the reader is referred to the excellent résumés by Drill published in 1952,[44] Moon in 1931,[143] Ottenberg and Spiegel in 1913[151] and Stoner and Magee in 1957[153] Among those chemicals which produce these affections are allyl formate, arsenic, chloroform, carbon tetrachloride, urethane, lead, silica, phosphorus, pyridine, silicon, bile salts, ethionine and selenium[4 28 29 37 38 40 51, 96 100 107,108 114,118 127,136-140 148 145 149 151 158 159 162 186 187 199] Whether

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"stream-lining phenomenon" by the injection of dye into the splenic and superior mesenteric vein.[74] Mann subsequently produced atrophy of the left lobe of the liver in animals following splenic injections of carbon tetrachloride.[129] Himsworth and Glynn found that necrosis and atrophy developed in the left lobe of the liver in rats fed deficient diets and, in this situation, injectable India Ink could be traced from superior mesenteric vein to right lobe of the liver and from splenic vein to the left hepatic lobe.[99-101] They concluded that in experimental nutritional deficiency nutrient is desired sufficiently from the portal vein by the right lobe of the liver but the left lobe becomes necrotic and atrophic due to inadequate amounts of nutrient.

Himsworth also claimed that the centrilobular necrosis produced in rats subjected to subcutaneous injections of carbon tetrachloride is due primarily to ischemia rather than to the direct toxic action on the hepatic cells.[99,101] Swelling of the hepatic cells and obstruction of circulation lead to ischemia of the hepatic cells. Massive hepatic necrosis was produced by complete arrest of intralobular circulation due to swollen hepatic cells causing intralobular congestion. Experimental cirrhosis is characterized by a distorted and anastomatic vascular led.[99,135] The hepatic blood vessels in cirrhosis are consolidated within the fibrotic areas (Chapter 3) as parenchyma gradually is destroyed. McIndoe has demonstrated that the hepatic cells are deprived gradually of their nutritious portal blood supply. Abnormal hepatic vascular pressure relationships develop in cirrhosis as the direct result of arteriovenous shunts, hypervolemia and hepatic, venous obstruction. As parenchymal damage persists, fibrosis continues and portal blood vessels are further constricted. Nodular regeneration also appears to distort hepatic vasculature. These vascular dynamics, as we shall see, further perpetuate hepatocellular impairment and are important factors in producing portal hypertension.

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THE NORMAL LIVER

That the liver cord concept was incorrect was proposed in 1918 by Hans Elias.[15] His histological studies of mammalian livers paved way for reinterpretation of the normal and abnormal structure of the liver (Figs. 1-5).[19-23] He applied an ingenious geometricostatistical technique and stereoscopic reconstruction to study the structure of the liver of vertebrates and demonstrated that the classical concept of the hepatic lobule consisting of cords of hepatic cells, two cells thick and supported in reticuloendothelium, was no longer tenable. He found that the liver consisted of one-cell thick plates which form a continuous mass of cells tunnelled by the labyrinth of the hepatic lacunae. Elias also disclosed that the cellular architecture of the mammalian liver consisted of four basic types of hepatic cells: octahedral, pentahedral, decahedral, and dodecahedral. The continuous mass of liver cells is arranged as laminae hepatis or liver plates and the spaces between the walls of the laminae were called the hepatic lacunae. The direction of the hepatic laminae is determined by the direction of the sinusoids and the blood pressure gradients. The ill-defined "hepatic lobules" which surround the central veins according to this concept are continuous with one another. "Muralium" was coined to describe the continuous wallwork of liver plates, which, as Hering showed in 1866, are perforated, making possible anastomoses between sinusoids.[24] These connect with one another to form the hepatic labyrinth and comprise the channels known as the "portal canals." Each canal contains a branch of the portal vein and hepatic artery, a network of bile ducts, lymphatics and nerves. This vast hepatic labyrinth extends uninterruptedly throughout the entire liver, suspended in which is a vast network of sinusoids, which are in contact on both sides by hepatic cell plates. Elias has shown that the mammalian liver is pervaded by two systems of tunnels, the portal and hepatic canals, which are separate and run perpendicular to each other. The portal canals appear as tunnels in the continuous mass of hepatic cells surrounded periportally by a limiting plate called the "lamina limitans." This consists of a uniform network of hepatic cells which are thinner and stain more heavily than the continuous

Chapter 5

MORPHOLOGY OF CIRRHOSIS

INTRODUCTION

ALMOST A CENTURY elapsed before there was modification of the morphological descriptions of the normal liver Gerlach in 1849 had taught that the hepatic cells were arranged in columns and Beale in 1856 mentioned that they were contained in a thin walled tube[7,23] Hering in 1866 showed that the liver of the rabbit was a continuous mass of cells tunnelled by capillaries and that the sinusoids were separated by a single layer of hepatic cells.[36] Kiernan described the hepatic lobule in 1833 in the pig, noting the central vein and portal triad, the latter containing the bile duct and the arterial and venous afferent vessels[42] Brissaud and Sabourin in 1888 demonstrated that the hepatic lobules centered around the portal canals in the seal[12] Mall in 1906 proposed the term "portal unit" as the basic structure of the liver and Arey in 1932 reported this morphological finding in other mammals.[3,53] Gerlach in 1849 and Andréjevic in 1861 were among the early observers to describe the network of bile canaliculi surrounding the hepatic cells[2,28] Kupffer in 1899 described the sinusoids and a network of fine argentaffin fibers located between the hepatic cells and the sinusoids[46,47] Kiernan in 1833 and Gerlach in 1849 were the early investigators to demonstrate that the hepatic artery supplies blood to hepatic tissue located in the portal areas and terminates in arteriolar networks about the bile ducts[28,42] The classic structure of the hepatic lobule was recorded in textbooks on histology to contain: (1) the sinusoids, the bile canaliculi, the limiting plate, the reticuloendothelial system including the Kupffer cells, the lymphatics, the nerves and cords of hepatic cells radiating like spokes of a wheel from a central vein peripherally, and (2) the portal area containing the bile duct, hepatic arteriole and the portal venule



FIG. 2. Stereogram illustrating the old theory of cords being two cells thick and wrapped in reticuloendothelium. (Courtesy, Elias, Hans, Ph.D., and Research, Vol. 37, G. D. Searle & Co.)

artery, which are not connected with the plexuses, empty into the sinusoids. These capillaries have sphincters, the activity of which modify the flow of blood to the sinusoids. The control of hepatic blood flow by inlet and outlet sphincters has been summarized by Knisely.[43,44] The mechanically strong biliary canaliculi form a network of polygonal meshes within the liver plate which connect to intralobular ductules and interlobular bile ductules. The interlobular ductules convey bile to the portal bile duct.[11,35] The communicating duct between the portal bile duct and the interlobular ductules in the limiting plate has been referred to as the *canal of Hering or periportal cholangiole.*[34,83]

It is known that a reticulum network of argyrophil fibers lie between the sinusoids and the liver cells. The walls of the sinusoids consist of two types of cells—flat endothelial cells and phago-

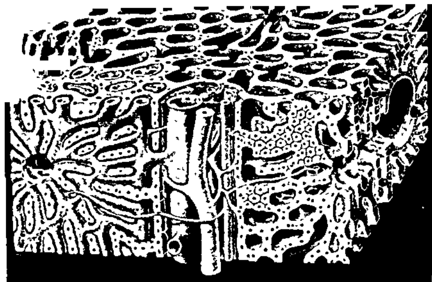


FIG. 1. Stereogram of the normal liver. Note extensive connecting unicellular liver plates enmeshed in a reticulum network, portal canal surrounded by limiting plate, containing portal vein, hepatic artery, bile ducts, lymph vessel, periportal connective tissue; ramifications of these vessels through the lacunae, portal vein connecting inlet venules to sinusoids and sublobular veins, perisinusoidal space of Disse and periportal space of Mall, arterial capillaries emptying into paraportal and intralobular sinusoids, bile canaliculi within liver plates connect intralobular cholangioles with cholangioles in portal canals. (Courtesy, Elias, Hans, Ph.D., and Research, Vol. 37, G. D. Searle & Co.)

intralobular liver cells.[63] A limiting plate in the liver is uniform, containing a network of bile canaliculi which surrounds the portal canals and hepatic canals and is continuous with the capsule of the liver.[29]

The bile ducts in the portal area are surrounded by a plexus of capillaries which connect the hepatic artery and the portal vein. The venules arising from the tributaries of the portal vein penetrate the limiting plate and connect with the sinusoids which supply blood to the central vein. The central vein empties into the sublobular vein, a tributary of the hepatic vein.[77] Elias demonstrated that arterial capillaries originating from the hepatic



FIG. 4. Stereogram showing the suspension of the sinusoidal network in the lacunae of the hepatic labyrinth. (Courtesy Elias Hans, Ph.D. and Research Vol. 37, G. D. Searle & Co.)

MORPHOGENESIS OF CIRRHOSIS

Most investigators now concede that the fundamental and characteristic morphological features of cirrhosis, which Kretz in 1905, Rossle in 1930, and de Josselin de Jong in 1931 emphasized, respectively, are necrosis of the hepatic cells, fibrosis, and nodular regeneration.[18,43,71] Emphasis on inflammation or fibrosis instead of nodular regeneration, controversial morphological criteria of chronic hepatitis and early cirrhosis, the original connotation of the term cirrhosis by Laennec and its Greek interpretation, the histological interpretation and implication of types of hepatic injury produced in experimental animals, and the comparison of specimens of liver obtained by needle biopsy or at necropsy has led to considerable disagreement on the definition of cirrhosis.[4,5]

cytes of Kupffer[43,44,46] Between the hepatic cells and the sinusoids is a tissue area known as the space of Disse, which connects with the periportal space of Mall.[53,63] These areas are intimately concerned with, but are not connected to the hepatic lymph vessels, which form networks in the portal canals and send narrow spurs into the delicate trabeculae which both the intralobular arterioles and the ductules are surrounded. Perfusion of lymph occurs into these respective spaces. Elias has also described vividly the morphology of various vertebrate livers and embrylogy of the liver His monographs should be read by any scholar of diseases of the liver for better interpretation of the morphology and histogenesis of cirrhosis



Fig 5 Stereogram showing the unicellular human liver plate the sacculosinusoidal type of liver as compared to the tubulounmodol type, which has less [illegible]

[illegible]

search, Vol 57, G D Searle & Co)

may be observed in patients with so-called latent or asymptomatic portal cirrhosis, hepatolenticular degeneration or hemochromatosis. Nodular regeneration may be localized as observed in focal cirrhosis.[9] It appears that the only unfailing morphological distinction of cirrhosis is nodular regeneration, which usually comprises the bulk of tissue in cirrhosis.[9,13,27,30,37,58,79] This morphological feature is probably related to the distortion of the lobular architecture and vascular relationships, and anastomoses between the branches of the portal and hepatic veins. It has been suggested that the main functional consequences of cirrhosis, which are necrosis or degeneration of the hepatic cells and the altered intrahepatic blood flow, are caused by nodular regeneration and by vascular anastomoses.[65,66] Morphologically, these features may explain hepatic insufficiency and portal hypertension. Ductular cellular reaction in the liver as the consequence of hepatic damage has recently been emphasized.[67]

It is worthwhile to review the different morphogenetic pathways which lead to cirrhosis irrespective of the causative factor. In 1955, Popper and Elias utilized the three-dimensional analysis and a statisticogeometric method to study the histeogenesis of cirrhosis.[19,21,26,65] They suggested that cirrhosis may result possibly from several processes: (1) collapse following massive and submassive necrosis; (2) portal and periportal inflammation; (3) central toxic necrosis; (4) passive congestion; (5) fatty metamorphosis, and (6) pericholangiolitis (inflammation around the smallest bile ducts). They demonstrated three architectural pathways in the histogenesis of cirrhosis (Figs. 6-11).

One pathway results from the sequelae of massive, submassive or repeated focal necrosis of the lobular parenchyma with subsequent collapse progressing to postnecrotic cirrhosis. When the collapse occurs the portal and hepatic canals become approximated leading to large areas of connective tissue, vascularized by old sinusoids. As a result there is a rapid transfer of blood from the branches of the portal vein and hepatic artery to the branches of the hepatic vein via the sinusoids. Traction occurs in the surrounding tissue as a result of collapse of the necrotic area and fissures arise in which connective tissue septa develop. Lobular

[8,17,31,38,39,40,48,49,51,52,54,55,58,64,65,79] In fact, Elias and Popper caution against conclusions drawn from experimental animals as to the morphogenesis of cirrhosis because of the difference between man and the rat in the distribution of the branches of portal and hepatic veins and the lymphatics.[25]

If nodular regeneration is recognized as the most important and essential feature of cirrhosis, many of the reported cases, for example, of syphilitic cirrhosis, primary and secondary biliary cirrhosis, cardiac cirrhosis or zooparasitic cirrhosis fail to meet the morphological criteria of cirrhosis. Moreover, histological examination of a hepatic specimen commonly reveals evidence of cirrhosis by the presence of nodular regeneration and fibrosis in the absence of necrosis or degeneration of the hepatic cells. This

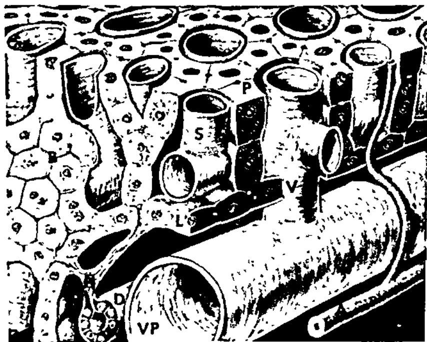


FIG. 5 Stereogram showing the relationship of the hepatic parenchyma to the biliary and vascular systems. A. Hepatic artery. B. Biliary canaliculi. D. Bile duct. H. *Canal of Hering*: L. Limiting plate; P. Intralobular parenchyma. S. Sinusoid. V. Inlet venule. VP. Portal vein. (Courtesy, Elias, Hans, Ph.D.—Transactions of the 11th Conference on Liver Injury—1952.)

fragments of tissue proliferate to form regenerative nodules of irregular sizes. These nodules also impair blood flow by compressing the intrahepatic blood vessels and, the more acute the necrosis the more intensive the regeneration. Acute necrosis also causes portal and periportal inflammation, potentially resulting in the formation of septum. Popper and Elias, also, noted that nodular regeneration was not uniform in various parts of the liver. The usual causes of postnecrotic cirrhosis are viral hepatitis, malnutrition in the tropics, and chemical hepatotoxins It is

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structure different from normal liver tissue. The cell plates in these nodules are predominantly two cells thick, resembling in their structure the livers of lower vertebrate animals. The afferent portal venules of such nodules are of normal caliber (13).

When two nodules which are healthy or vigorously growing are located near one another, they may tear apart a connective tissue septum that originally separated them (14), and fuse (15).

Vigorous growth of nodules results in flattening of the hepatic veins (16 17, 18)

This flattening of the hepatic veins (18) in turn seems to produce stasis in the interior of certain nodules accompanied by necrosis of the liver cells in the center of the nodule (19)

In a later stage the dead cells are replaced by collagenous tissue (20) This degenerative process proceeds from the center toward the periphery, until even the peripheral cells become small, isolated and dark staining (21).

Small flat groups of flat, dark staining cells (22) are found near or at the periphery of numerous nodules Their significance is unknown

In some nodules liver plates are found similar to duct epithelium in appearance (23) These are broad, flat sheets, two cells thick with a lumen between both cell layers It is not known whether these ductoid sheets are con nected with real ducts

While many of the hepatic veins become flattened, many of the portal veins remain cylindrical (24) Their terminal branches are arranged in a basket like fashion around the nodules

The smallest, intraseptal branches of the portal vein show a tortuous course (25). Numerous anastomoses between these and intraseptal radicles of the hepatic veins (26) exist

The branches of the hepatic artery (27) remain straight Anastomoses between arteries and small portal branches occur (28).

From the connective tissue septa (29), thin fibrous membranes (30) arise By the contraction of their leading edges these membranes advance into the parenchyma, cut nodules in two and distort the efferent venules of the nodules (Courtesy, Elias, Hans, Ph D and Flint, Eaton & Co)



Fig. 6 Stereograms on Cirrhosis

In this specimen we find small groups of large liver cells (1), many of which divide amitotically Some flat, darker staining cells are seen at the periphery (2) The group is surrounded by a peripheral, venous sinus which is connected with an internal capillary network

These small groups probably grow and develop into larger nodules, such as the one slightly to the left of the center The periphery of this nodule is occupied by large, amitotically dividing cells which constitute a blastema (3) This blastema is a solid mass of cells, several cells thick It is vascularized by very narrow portal capillaries (4) and by arterial capillaries (5)

Toward the center of the nodule the capillaries become wider and resemble normal sinusoids (6) The liver cells are arranged between these vessels in two cell thick walls (7)

In the very center of the nodule the cells are arranged in one cell thick plates (8). In other words, the normal architecture of the liver is restored at this place The nodules are drained by efferent venules (9). There is no evidence that these are identical with the central veins of normal liver lobules.

Bile canaliculi of normal appearance are seen between the numbers 10 and 8 They drain into cholangioles (11), which in turn drain into ducts (12).

Other large nodules are of even construction throughout. They appear to be well balanced and rather healthy (13). These nodules, however, have a

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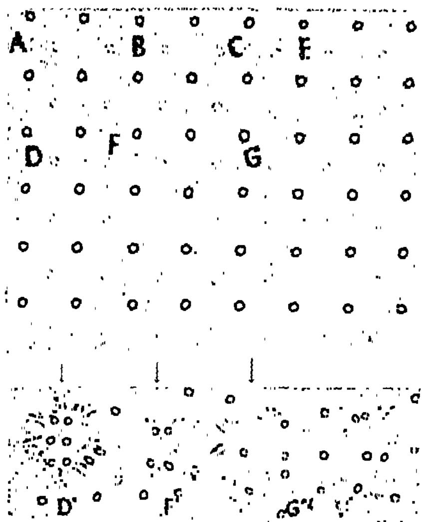


FIG. 7. Diagram of types of hepatic necrosis Portal canals heavy circles, central fields, light circles A Focal necrosis, B Central necrosis, C Periportal necrosis, D. Massive necrosis, E Central bridging F. Submassive, sectional necrosis of a remaining fragment of lobule, G Multilobular fragments (F and G drawn by Elias, Hans, Ph D – Am J Med – 1954)

FIG. 8. Diagram of types of collapse (drawn by Elias, Hans, Ph D). Portal canals, heavy circles, central fields, light circles. D¹, following massive necrosis, F¹, following submassive necrosis, the nodules being fragments of one lobule, G¹, multilobular nodules. (Courtesy Popper – Am. J Med – 1954)

found in patients with hepatolenticular degeneration and commonly in infants and children. It has been suggested that cardiac cirrhosis, while rare, develops in the manner of toxic cirrhosis.[63, 65, 67, 72]

The second pathway leading to portal, Laennec's or septal cirrhosis is by the primary formation of septa by aggregation of collagenous material from the portal triad, from the central canal or within the lobular parenchyma. Septa form either in the lobular parenchyma as reinforcement of the network of reticulum or in stress fissures separating hepatic territories of uneven expansion. The stimuli for the formation of these septa are focal necrosis, fatty metamorphosis and irregular regeneration. This

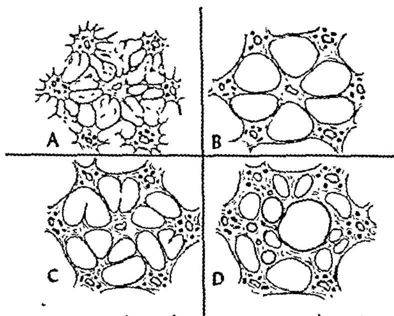


FIG. 9. Diagrams of nodule formation by septa. A. Membranes radiating from portal and central fields. B. Membranous tracts aggregate to form septa which subdivide the lobule. (A and B Courtesy Elias, Hans, Ph.D.—Transactions of the 11th Conference on Liver Injury—1952.) C. Further subdivisions of lobular fragments (nodules) by septa. D. Regenerating nodules obscure original architecture. (C and D Courtesy Popper and Elias—Am. J. Path.—1955.)

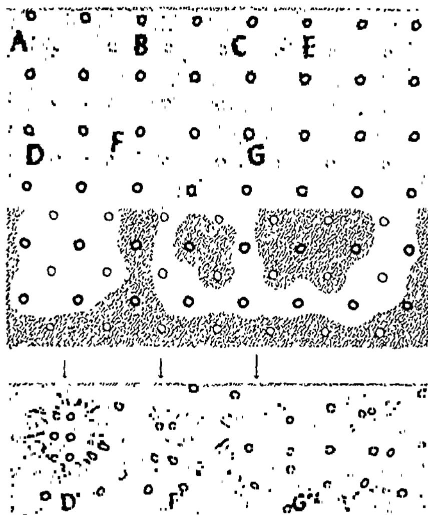


FIG. 7. Diagram of types of hepatic necrosis Portal canals, heavy circles, central

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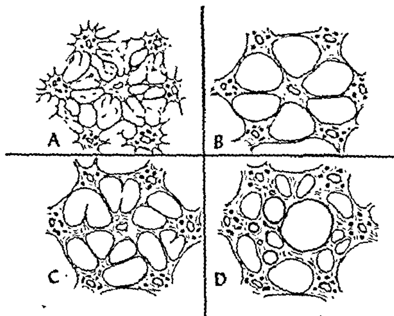


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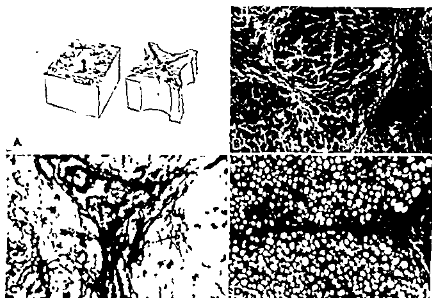


FIG 10 A. Schematic drawing of massive necrosis of several hepatic lobules, followed by collapse of the necrotic area and breaks in the surrounding noninvolved tissue B Fissures in the lobular parenchyma bordering on an area of recent postnecrotic collapse Hepatic cells are disappearing around dilated sinusoids in the fissures (H & E, x 70) (Courtesy, Popper, Elias, and Petty—Am J Clin Path—1952) C Micromembranes radiating from portal triad into lobular parenchyma in septal (portal) cirrhosis (Van Giesen x210). D Straight septum extending from portal triad in fatty cirrhosis (Mallory X60) (A, B, and D, Courtesy, Elias, Hans, Ph D—Transactions of the 11th Conference on Liver Injury—1952)

type of cirrhosis may be the result of malnutrition (alcoholism) or viral hepatitis In contrast to massive or submassive necrosis of the lobular parenchyma, stimuli for the septum formation have a tendency to be uniform throughout and involve all the lobules Popper has proposed use of the term "primary septal cirrhosis of multiple causative factors" since the primary septum formations in these instances cause subdivision of the lobule and formation of regenerative nodules Marked rearrangement of the liver cell plates, formation of a new efferent vein and regeneration develops in the nodule. The latter is reflected in liver cell plates several cells thick and in the formation of ductules In fatty

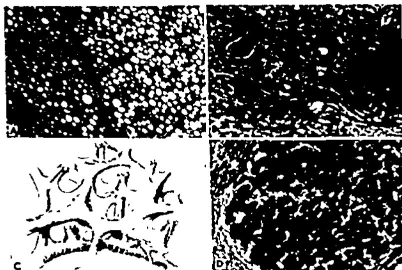


FIG 11 A Fissure in fatty cirrhosis apparently developed as a result of (nutritional?) stress (H & E, x90) B Cholangiolitic (trabecular) cirrhosis Trabeculae containing proliferated cholangioles are surrounded by fibers (Van Gieson x180) C Schematic drawing depicting septa extending between the portal and central canals which cross in the three-dimensional space D Cirrhotic regenerative nodule revealing several-cell thick plates in its periphery and unicellular thick plates centrally (Mallory x 150) (Courtesy, Elias, Hans, Ph D —Transactions of the 11th Conference on Liver Injury—1952)

metamorphosis, septation may result from collapse of fatty cysts, periportal or intralobular necrosis and inflammation, and membrane formation in stress fissures as the result of uneven expansion of hepatic territories from irregular deposits of fat, regeneration and necrosis The evolution of fatty cirrhosis (alcoholic) has been traced by Zimmerman in four stages: steatosis, steatonecrosis, steatocirrhosis, and cirrhosis[80] Popper and Elias suggest that cirrhosis does not result directly from fat deposition, but from increased susceptibility of the fatty liver to necrotizing or inflammation processes which eventually produce regeneration [65,84] This is in contrast to the experimental studies of fatty metamorphosis in animals as the result of choline deficiency (Figs 12, 13).[10,32,35]

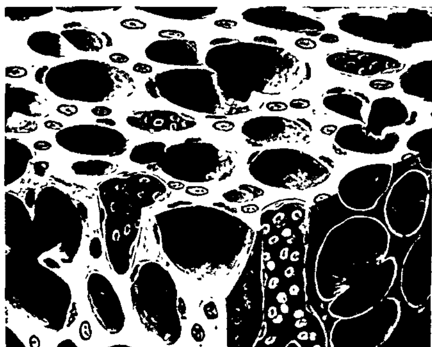


FIG 12 Stereogram of fatty liver showing lipodiastemata (cavities resulting from coalescence of fatty hepatic cells and the intervening pseudosyncytium (Courtesy, Elias, Hans, Ph D —Stereograms on Cirrhosis and Fatty Liver—Flint Eaton & Co —1951)

The third morphogenetic pathway of cirrhosis is characterized by the extension of fibrous connective tissue around the perilobular and intralobular ductules, referred to as pericholangitis This produces a cylindriform network or trabeculae traversing but not dividing the lobule. This pattern may be observed in patients with cholangiolitic hepatitis or cholestatic hepatic disease. In the late stages septum are formed dividing the lobule, and progression to cirrhosis occurs.[1,52,60,71,79] These authors, therefore, suggest that the three morphogenetic pathways, namely, collapse, septum formation, and cylindriform trabeculae may terminate in a common manner with extensive development of septa and regenerative nodules, for which they advocate the term, "Laennec's cirrhosis."

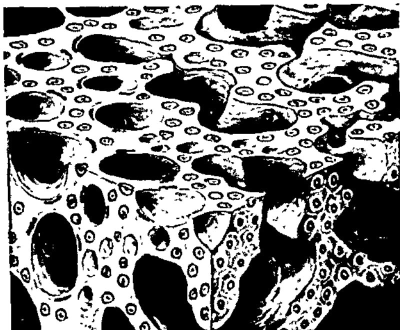


FIG. 13 Stereogram showing regenerated (not nodular) fatty liver The pseudosyncytium (*upper left*) changes into two-cell thick plates (*right*) (Courtesy, Elias Hans Ph D—Stereograms on Cirrhosis and Fatty Liver—Flint, Eaton, & Co—1951.)

Popper and Elias regard the basic morphological features of cirrhosis to be nodular regeneration and vascular anastomoses between the portal and hepatic veins[65] The liver is dissimilar, in one aspect, to many organs of the body such as the brain, heart and skin, which restore cellular necrotic injury particularly by the formation and condensation of fibrous connective tissue Repair of hepatic cellular necrosis by regeneration of the hepatic cells constitutes an unusual morphological characteristic of the hepatic cell. This individualistic, structural feature of the hepatic cell can be appreciated when hepatocellular necrosis may heal by regeneration either with complete restoration or in the form of nodules or pseudolobules, characteristic of cirrhosis One may suspect, on this basis, the autonomous, embryonic nature of the

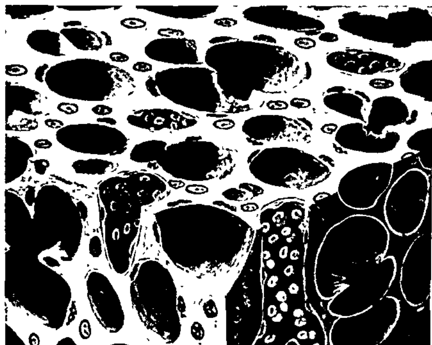


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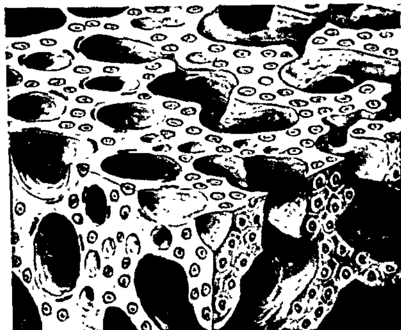


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hepatic cell. Elias investigated the development of the liver in vertebrates and arrived at some remarkable conclusions as follows: no invertebrates exist which possess a true liver such as all vertebrates do ("Hepatata"), the liver is a muralium or substitute yolk sac, situated between the veins supplying the in-

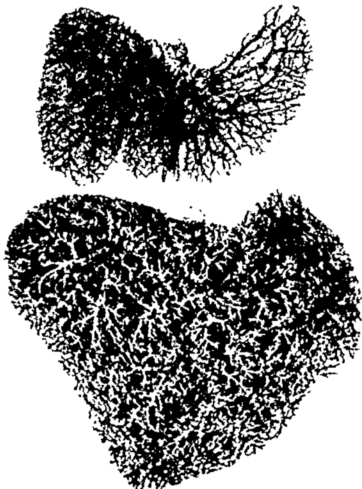


Fig. 14 Distorted, collapsed vascular tree in portal cirrhosis Celloidin casts demonstrating portal and hepatic venous systems Portal cirrhosis (*upper*), and normal liver (*lower*). Marked reduction in vascular bed in cirrhosis (Courtesy, McIndoe—Arch Path—1928)

testine and the venous side of the heart, the primary function of which is the storage and remobilization of nutritive substances the liver of all vertebrates except the lamprey is remarkably uniform in structure; contrary to von Baer's first and second laws of embryogenesis, the liver of every small group of vertebrates sets out in an independent manner to develop a liver, and from these diverse beginnings an identical end-product is formed; the biogenetic law of Muller and Haekel, which postulates that embryos resemble ancestral adults, does not apply to the liver; finally, the muralium is the only structure suitable for performing the various functions of the liver. 'Uniformity of structure based on uniformity of development may be accidental, but, if there is uniformity of functional structure arising from diversified beginnings, one must suspect that the liver, as far as its histological structure is concerned, is close to perfection."[20-23]

Baggenstoss suggests in the following manner that the re



FIG. 15A. Side view of wax model constructed on glass base. A small vein in right foreground passes over a portion of a regenerative nodule. This vein conforms to the outline of this nodule. (Courtesy Kelty, Baggenstoss and Butt —Gastroenterology—1950.)

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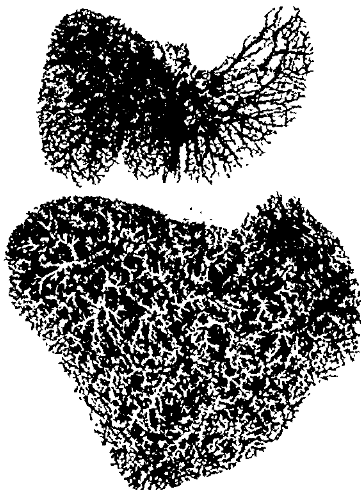


FIG. 14 Distorted, collapsed vascular tree in portal cirrhosis Celloidin casts demonstrating portal and hepatic venous systems Portal cirrhosis (*upper*), and normal liver (*lower*). Marked reduction in vascular bed in cirrhosis (Courtesy, McIndoe—Arch Path—1928)



Fig 1 ... regenerative nodules over ...nective tissue (×3 ?)
Fig 1(...ans veins by regenerative nodules These two veins are rep...cated in the wax model (Figure 15) (A and B, Courtesy, Kelty, Baggenstoss, and Butt—Gastroenterology—1950)



FIG 15B Top view of the wax model Regenerative nodules have compressed the wall of a large vein These reconstructions suggest that blood vessels in the cirrhotic liver are narrowed and obliterated by the pressure of growth and expansion of the regenerative nodule against the adjacent rigid connective tissue (Courtesy, Kelty, Baggenstoss, and Butt—Gastroenterology—1950)

generative nodule develops following hepatic necrosis by proliferation of the available hepatic cells accompanied by a new framework of reticulum and sinusoids [5] Regenerative nodules may also form as the result of the hepatic lobule being subdivided by *septums*, particularly those connecting the central and portal canals, and by proliferation of hepatic cells in areas of periportal necrosis surrounded by connective tissue.[69] Baggenstoss has also stated that the proliferating hepatic cells push aside the old framework of reticulum and sinusoids where they condense as a scar or fibrosis.[5,41,74] The fully developed regenerative nodule,



Fig 1 [illegible] regenerative nodules over [illegible] connective tissue (x3.5)

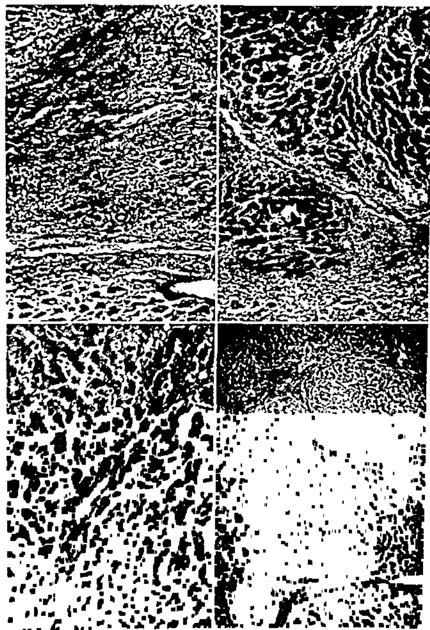
Fig 1b [illegible] ...atis veins by regenerative nodules These two veins are re[illegible]...nted in the wax model (Figure 15) (A and B Courtesy, Kelty, Baggenstoss, and Butt—Gastroenterology—1950)





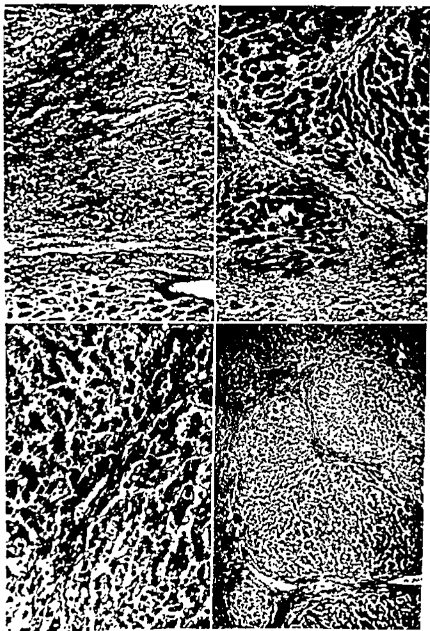
FIG. 18 Vinylite cast of a human liver with portal cirrhosis injected with yellow vinylite through the portal vein and with blue vinylite through the vena cava. (*upper*) photograph of portal varicosities and basket formation near the coronary ligament. Distortion of the vascular tree (X5) (*lower left*), drawing showing the basket formation of portal branches and flattening of tributaries of hepatic vein (*lower right*) drawing of anastomoses between branches of portal vein (light) and tributaries of hepatic vein (black) at the dorsal surface of the liver near the falciform ligament (Courtesy, Popper, Elias and Petty—Am J Clin Path—1952)

FIG. 17 Thick frozen sections of cirrhosis in humans revealing extensive anastomoses between branches of portal and hepatic veins located in septa (*upper*) Postnecrotic cirrhosis injected with Berlin blue gelatin through the portal vein (*appearing grey*) and with India ink through the hepatic vein (*appearing black*) (X150) (*Lower*) portal cirrhosis injected with opaque red ink through the portal vein (appearing white) and with India ink through the hepatic vein (appearing black) Combined transmitted and incidental lighting (X200) (Courtesy, Popper, Elias, and Petty—Am J Clin Path—1952)



which is usually spherical, oval or, more rarely, garland shaped, compresses the adjacent connective tissue, bile ducts and blood vessels. The compressed connective tissue, unable to expand, may become collagenized (Fig. 11). According to some observers, portal hypertension occurring in cirrhosis is the result of constriction of the branches of the portal vein by fibrosis, and, according to others, by vascular shunts between branches of the hepatic artery and portal vein. Portal hypertension in the cirrhotic liver can be explained by the destruction of the original capillary bed, and the massive distortion of vessels and vascular relationships as the result of the regenerative nodule. The latter distorts the course of the hepatic vein and compresses the collapsed sinusoids.[41,65,66,73,74] Kelty, Baggenstoss, and Butt improvised a glass plate preparation and constructed a wax model to depict the contour of the intrahepatic vascular framework of the regenerative nodule.[41] The morphological appearances of the regenerative nodules in portal and postnecrotic cirrhosis suggest a different histogenesis of these two conditions (Figs. 15, 16).[6,73,74] It has been postulated that the course, large, irregular regenerative nodules observed in postnecrotic cirrhosis represent vigorous regeneration on the part of a few intact islets of hepatic cells which survive after massive necrosis of the liver, particularly in the younger individual. The parenchyma of these regenerative nodules resembles normal liver except for the presence of distorted columns of cells, displaced hepatic vein, and absent portal triads. On the other hand, the appearance of the concentric, granular regenerative nodules present in portal, Laennec's, or septal cirrhosis suggests less active

Fig. 19. (*Upper left*) broad connective tissue septum as the end result of collapse in postnecrotic cirrhosis containing many vessels of venous character which represent transformed sinusoids of the lobular parenchyma which has disappeared. (Van Gieson's x100). (*upper right*), fissures in the lobular parenchyma of a section of recent postnecrotic collapse. In region of fissures note loss of hepatic cells about the dilated sinusoids. (H & E x70). (*lower left*) sinusoids are included in a newly formed septum in portal cirrhosis while surrounding hepatic cells disappear. (Van Gieson's x150). (*lower right*) central and portal canals are connected by septa containing vessels in portal cirrhosis. (Van Gieson's x30). (Courtesy, Popper, Elias and Petty—Am. J. Clin. Path.—1952.)



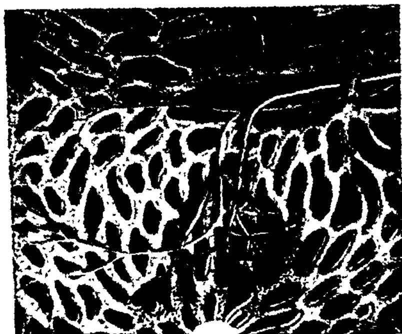


FIG. 21. Reconstruction from serial sections showing the intralobular arterioles and arterial capillaries. These empty into the central sinusoids. The arterial capillaries have sphincters. The intralobular ducts form loops.

artery (Figs. 17-21).[45,55,75] Naturally occurring porta-venous shunts are presumed ineffective in reducing portal hypertension, possibly because compression of the hepatic veins by the regenerative nodules occurs more proximal to the heart than do these anastomoses. In a study of human and rat livers Popper, Elias and Petty have demonstrated, by injecting the portal vein and hepatic artery and vein with colored material, that these anastomoses shunt blood from the portal vein to the hepatic vein and by-pass the lobular and nodular parenchyma.[66] In this manner circulatory impairment of this parenchyma occurs, reducing further hepatocellular function by diminishing the availability of nutrition and oxygen, and perpetuating central necrosis, collapse and eventually cirrhosis, unrelated directly to the original pathogenetic factor. The presence of these porta-venous anastomosis eventually may in-

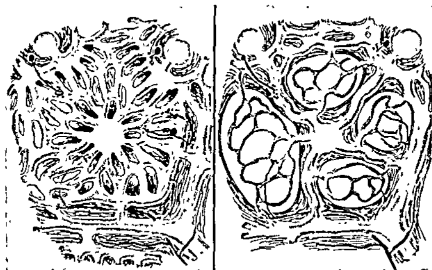


FIG 20 Diagram illustrating the origin of porto-hepatic venous shunts during division of a lobule into different nodules in cirrhosis Central vein in middle; portal veins in periphery, hepatic artery is small vessel adjacent to peripheral portal vein, (*left*) sinusoids and (*right*) porto-hepatic shunts that originated from a sinusoid by inclusion into a system, light areas in the right diagram are the regenerative nodules (Courtesy Elias, Hans, Ph D —Transactions of the 11th Conference on Liver Injury—1952)

regenerative capacity from groups of hepatic cells in each hepatic lobule as might be anticipated in older individuals The smaller, regenerative nodules are more structurally effective in compressing the hepatic veins Consequently, it has been shown that the finely nodular portal cirrhosis induces a greater degree of portal hypertension than the coarsely nodular postnecrotic cirrhosis, in which the clinical features of hepatic insufficiency predominate.[6,41]

Finally, porta-hepatic venous anastomoses or internal Eck fistulae develop in the cirrhotic liver by the transformation into veins of the remaining sinusoids included in the septums.[67,68] Or conceivably these may develop by angiogenesis, the formation of new vessels as the result of granulomatous inflammation.[59,60,70] These anastomoses occur more frequently than anastomoses between branches of the portal vein or portal vein and hepatic



FIG. 21 Reconstruction from serial sections showing the intralobular arterioles and arterial capillaries. These empty into the central sinusoids. The arterial capillaries have sphincters. The intralobular ducts form loops.

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duce progressive development of an irreversible stage of cirrhosis. When this occurs hepatic insufficiency or hepatic cellular necrosis may develop with ease as a result of hepatic anoxia, for example, from infections, hemorrhage or congestive heart failure. Another contributing cause suggested by McIndoe for maintaining portal hypertension in the cirrhotic liver is the increased arterial blood flow to the liver.[57] This is the result of mechanical impairment of intrahepatic portal blood flow causing enlarged anastomoses between the hepatic artery and portal vein.

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Chapter 4

NEEDLE BIOPSY OF THE LIVER

INTRODUCTION

BECAUSE OF the unique role attached to needle biopsy of the liver in the histological diagnosis and pathogenesis of cirrhosis in living patients, an appraisal of the diagnostic indications and limitations of this technique is necessary One of the reasons for the renewed interest in disease of the liver, particularly in the past twenty years, has been the use of needle biopsy of the liver as a diagnostic technique Although accurate information derived from a thorough history and physical examination is unparalleled in importance in the adequate diagnosis of hepatic diseases, information derived from various hepatic function tests and needle biopsy of the liver may afford supplementary information Since reports of this technique by Lucatallo in 1895 and Iversen and Roholm in 1939, it has received widespread use and acceptance as indicated by the large number of published reports[33,53] Although the initial enthusiasm for needle biopsy as a clinical tool necessary for the correct diagnosis of any type of hepatic disease has subsided, its discriminate and careful use in arriving at a diagnosis or in following the course of a certain hepatic disease, despite minimal morbidity, has been accepted generally by the clinician

Two types of needles are employed at present for hepatic biopsy, namely, the aspirating needle, its adaptation the Terry needle, and the punch needle (Figs. 1, 2) [3,11,14,24,27,29,33,39,49,68,76,77,87,91,95,103,107,110] Of these two types the punch or Silverman needle has been the most popular because of its low cost, safety and practicality *This needle consists of a thin split inner needle which can be* inserted into a shorter 14-gauge outer needle. It has been observed that more satisfactory and longer biopsies may be secured if the inner needle protrudes approximately 3 cm from the tip of the outer needle. In this manner the major disadvantage of the use of the punch needle is overcome. The punch needle actually

dissects a core of hepatic tissue whereas the aspiration needle withdraws the specimen by suction. There are various types of suction needles. Among the most popular and practical modification of the Gillman needle is the Terry needle which contains a single syringe for suction to which is connected a beveled needle of varying size.[303] The disadvantages of the latter instrument appear to be the expense, and the time and technique involved in applying suction to the syringe, and the possibility of sizable penetration and laceration of the hepatic capsule. On the other hand, these are minimized by the Terry needle. The advantage of the suction needle lies in the greater width and length

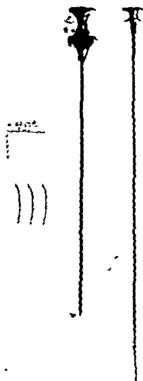


FIG. 1. Modification of Vim Silverman needle. Representative processed section on microscopic slide (maximum length)

Chapter 4

NEEDLE BIOPSY OF THE LIVER

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Two types of needles are employed at present for hepatic biopsy, namely, the aspirating needle, its adaptation the Terry needle, and the punch needle (Figs. 1, 2).[5,11,14,21,27,28,33,39,48,68,76,77,87,94,95,103,107,110] Of these two types the punch or Silverman needle has been the most popular because of its low cost, safety and practicality This *needle consists of a thin split inner needle which can be* inserted into a shorter 14-gauge outer needle It has been observed that more satisfactory and longer biopsies may be secured if the inner needle protrudes approximately 3 cm. from the tip of the outer needle. In this manner the major disadvantage of the use of the punch needle is overcome The punch needle actually

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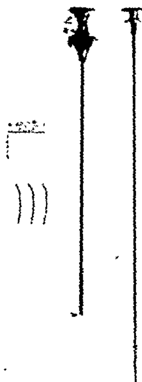


FIG. 1. Modification of Vim Silverman needle. Representative processed section on microscopic slide (maximum length).

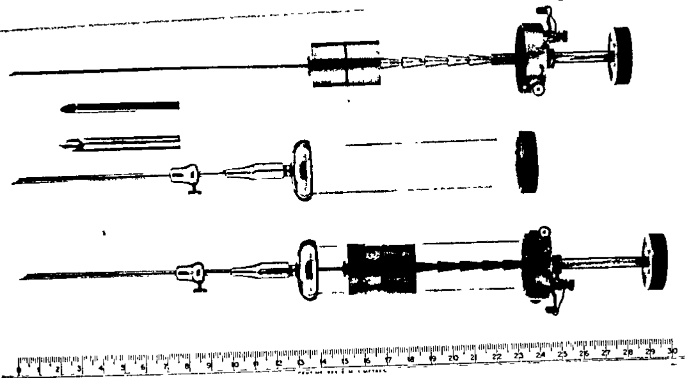


Fig 2 Aspiration needle for liver biopsy, the Terry modification of Gillman needle (Courtesy Terry, Richard B)

of the biopsy obtainable. In no instance should the neophyte perform a needle biopsy of the liver without thorough instruction or supervision. I have recommended to students who wish to learn this technique that they understand the anatomy in the operating area and obtain practice on a cadaver. Adequate biopsies by needle usually depend on mastering precise and careful instrumental technique. In this way needle biopsy of the liver will become even more popular as a diagnostic tool, serve to secure large specimens of liver, and be attended with less morbidity and mortality. Opinion is unanimous that this technique does not end with removal of the specimen from the patient. It is also necessary to become familiar with the mechanics of the instrument and maintain its care; understand the indications, contraindications, and complications of needle biopsy; exercise proper preoperative and postoperative care of the patient, and acquire necessary knowledge of hepatic histology in order to identify the specimen. It is regrettable that the use of needle biopsy of the liver has declined or has never been popular in some medical institutions in this country. That needle biopsy is not popular appears to be the result, as we shall see, of individual experience of the diagnostic limitations afforded by this technique. Such experience may have been occasioned by its unwarranted use in establishing a histological diagnosis of most cases of hepatic disease or hepatomegaly, the result of repeated failures to obtain satisfactory tissue, and the incidence of complications and deaths resulting from needle biopsy. In cases involving the latter skill and experience usually play a major role.

TECHNIQUE OF PUNCH BIOPSY

(1) A special tray containing the following sterile items: needles, hypodermic—No. 22-gauge 2-inch and No. 22-gauge spinal, scalpel, 1-ounce medicine glass; 1 cc. and 5 cc. syringe, 4" x 4" and 2" x 2" gauge, 4 small towels and the needle (Fig. 3).

(2) The biopsy is performed in the hospital in the patient's bed with the patient lying supine near the edge of the bed and in a fasting condition.

(3) Meperidine hydrochloride 50 mg. or pentobarbital 0.1 gm. is administered hypodermically about thirty minutes before the time of the biopsy for the purpose of sedation.

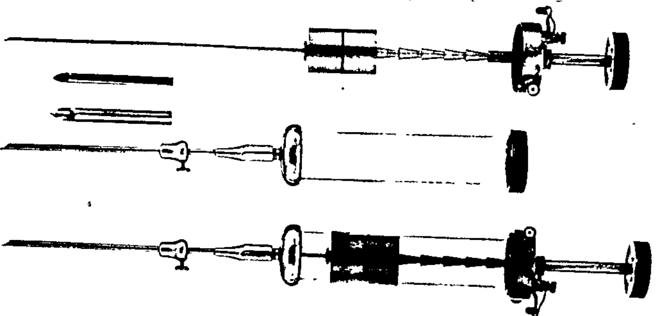


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The liver is percussed and palpated in order to determine its size If a palpably enlarged liver extends 3 cm. or more beyond the costal margin, a subcostal approach is employed In this situation the route of the biopsy should be along the right midclavicular line just below the costal margin with the needle directed about 30 degrees cephalad In other cases an intercostal route is selected This interspace, usually the 8th or 9th, is determined by the maximal amount of dullness overlying the liver The route of the biopsy is usually along the right anterior axillary line with the needle held parallel

(5) The area chosen for the biopsy site is cleaned by ether or alcohol after which an antiseptic agent, usually merthiolate or iodine, is applied Following this, sterile towels are draped about the biopsy site

(6) *A skin wheal is then made at the site with 1 to 2 per cent procaine or xylocaine,* following which the deeper tissues are infiltrated. If the route selected for the biopsy is subcostal,

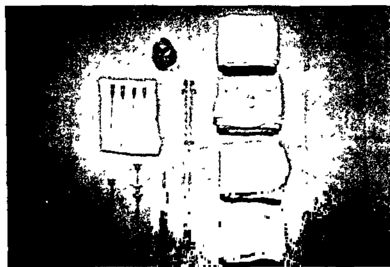


FIG 3 Contents of a sterile tray for needle biopsy of the liver. Four sterile towels (18" x 18"), 10 cc. syringe, scalpel, Vim Silverman needle and obturator; 4 needles (No 25 hypodermic; 2 inch No. 22 needle, No. 20 and No 23 spinal needles), 30 cc. bottle containing 10 per cent formaldhyde; gauze (1" x 1" and 2" x 2").

the patient is instructed to inhale deeply and hold his breath. In the event the intercostal route is selected, the patient now exhales and holds his breath. At the same time, the deeper tissues and hepatic capsule are anesthetized carefully, following which a small incision in the skin is made at the site of the biopsy. Further progress should be delayed if bleeding in encountered.

(7) The Vim-Silverman needle is now assembled by placing the inner split needle in the outer needle. The tip of the inner needle should extend just to the tip of the outer needle. Next, the above-described breathing maneuver is repeated and the needle carefully inserted into the liver, usually to a distance of about 1½ inches from the skin, and held firmly by 2 or 3 fingers from one or both hands. The extent of penetration, of course, depends upon the amount of subcutaneous deposit of fat. At this distance the inner needle is advanced to the fullest extent, following which the outer needle is again advanced 1 to 1½ inches. It is feasible to hold each of the needles steady with each hand during these important procedures. It is my custom next to rotate the inner needle around 360 degrees and to withdraw both needles in a slightly different angle

(8) The needles are now separated and the biopsy is then removed quickly and carefully from the inner needle without damage to the tissue. The biopsy is now grossly inspected and fixed in 10 per cent formaldehyde or Bouen's solution[11]

(9) Immediately following withdrawal of the needles, the attending nurse or operator should tamponade the site of the wound for several minutes. A surgical dressing is now secured tightly anteriorly and posteriorly from the midline by several wide strips of adhesive tape. The patient is instructed to lie quietly for 8 to 12 hours and to remain in the hospital overnight. The pulse and blood pressure of the patient are checked every fifteen minutes for one hour, then every thirty minutes for six hours and every hour until ambulation is permitted

CONTRAINDICATIONS OF NEEDLE BIOPSY OF THE LIVER

Actually any conceivable circumstance in which penetration of a needle 1 to 3 mm in width constitutes a hazard to life should

be considered a contraindication to the use of needle biopsy. As mentioned previously, this implies that the operator is adequately trained, experienced and confident[68] The following conditions arrived at by the experience of many investigators should be considered as risks to needle biopsy of the liver:

(1) *Inability of the Patient to Co-operate.* Because the patient must be able to control his respiration and adhere to simple instructions, the presence of hysteria, psychosis, delirium, stupor or coma contraindicates needle biopsy.

(2) *Potential Postbiopsy Hemorrhage* Needle biopsy of the liver should never be performed, except under unusual circumstances, in the presence of certain conditions which tend to increase the risk of postbiopsy hemorrhage. Such conditions are defective or unsharpened needles; physical findings of hemorrhagic tendencies, laboratory evidence of defective hemostasis, such as, hypoprothrombinemia, thrombocytopenia, abnormal bleeding and coagulation times or afibrinogenemia. Generally, a prothrombin time of the blood of 50 per cent or more is considered pertinent for safe needle biopsy[120] Only in the event that needle biopsy is essential for a histological diagnosis of the liver in order to more effectively treat the patient should these conditions be waivered Furthermore, it is advisable to consider the necessity of the administration of vitamin K parenterally before biopsy, particularly in patients who have been treated with broad-spectrum antibiotics, who have obstructive jaundice or who have sprue If bleeding from the initial skin incision persists in patients despite normal values of bleeding and coagulation times, prothrombin time and platelet, the procedure should be abandoned.[87, 101, 122] Anemia has been considered as a contraindication to biopsy[87] The importance of performing a biopsy of the liver with a perfect, sharp and easily maneuverable needle cannot be over-emphasized in order to reduce the possibilities of unnecessary laceration of the hepatic capsule, leakage of bile, pain, securing insufficient tissue and the necessity of repeated biopsy.

(3) *Hydrothorax, Pleuritis or Pulmonary Disease of Right Thorax.* These conditions may be aggravated or produce infec-

tion of malignant seeding in the peritoneum or liver when the intercostal route is employed for needle biopsy of the liver

(4) *Ascites, Subdiaphragmatic Abcess and Peritonitis.* Needle biopsy performed under these conditions may disseminate infection or fluid locally or in the right thorax. In order to determine effectively the size of the liver by percussion and palpation in the presence of significant ascites, an abdominal paracentesis should be performed prior to needle biopsy of the liver

(5) *Chronic Obstructive Jaundice and Hepatic Abcesses and Cysts* Prolonged obstruction of the extrahepatic bile ducts eventually produces intrahepatic bile stasis, elevation of intrabiliary pressure and hydrohepatosis Needle biopsy of the liver performed under these circumstances facilitates leakage of bile into the peritoneal cavity The possibility of dissemination of infection or parasites, hemorrhage and leakage of bile intrahepatically or into the peritoneum renders needle biopsy hazardous in patients with suppurative or amebic hepatic abcesses or parasitic, retention or congenital cysts of the liver

COMPLICATIONS OF NEEDLE BIOPSY OF THE LIVER

Reactions, complications and fatalities occurring as the result of needle biopsy of the liver have been reported in several instances, further emphasizing the contraindications of this technique As greater experience and more perfect technique in performing these biopsies, have developed the incidence of the morbidity and mortality from needle biopsy of the liver has decreased and become stable The irreducible incidence of complications as the direct result of needle biopsy should be viewed in light of the fact that this technique should be considered a "blind procedure." In reports of large series of needle biopsies the incidence of complications has varied from 0.2 to 50 per cent and of mortality from none to nearly 0 5 per cent [10,14,22,24,28,29,37,38,39,43,78,87,100,103,107,110,123] Zamcheck's group reviewed 20,016 needle biopsies of the liver in 1953 and calculated a gross mortality of 0 09 per cent (17 cases) [123,124] The complications of needle biopsy of the liver consist of the following

TABLE 1

COMPLICATIONS OF 632 NEEDLE BIOPSIES OF THE LIVER

	(1950–1953)	(1954–1957)
Number of needle biopsies	158	474
Postbiopsy pain	34	83
"Pleural shock"	8	11
Unsuccessful attempts	6	7
Bile peritonitis	2	4
Death	1	0
Abdominal surgery	2	4
Gallbladder perforation	0	1
Negative findings	0	1
Hemoperitoneum	0	2
Abdominal surgery	0	1
Negative findings	0	1
Blood transfusions	0	2
Pneumothorax	1	0
Right hydrothorax	1	0

(1) *Local and Referred Pain* This may occur in approximately 15 per cent of patients It persists for a period of time and is controlled by analgesics or the intravenous administration of 200 mg of tetraethylammonium chloride [28 39 44 53] Pain commonly follows the intercostal technique for several hours, and may be related to insufficient anesthesia, the patient's anxiety or failure to co-operate, finesse of the operator's technique, subcapsular hemorrhage, trauma as the result of a defective needle or multiple biopsies and disregard of specific contraindications The usual sites of pain are the biopsy area, right hypochondrium and the right supraclavicular area, the latter being the result of diaphragmatic irritation

(2) *Peritoneal, Pleural or Subcapsular Hemorrhage.* This is usually the result of perforation of distended portal or hepatic veins aberrant arteries or intercostal arteries, hemorrhagic tendencies, hypersplenism or specific diffuse diseases of the liver, such as, hemangiomata, metastasis or peliosis hepatitis (Fig. 4) [18 28 39 101 124] Hemorrhage usually persists for no longer than 18 to 24 hours after biopsy and ordinarily ceases spontaneously In Terry's series of 7,532 biopsies, significant hemorrhage occurred in 16 instances (0 2 per cent) and laparotomy in 4 cases [103 105] Twenty-five of thirty-nine fatal cases attributed to needle biopsy in Zamcheck's series of 20,016 died as the result of hemorrhage.[123]

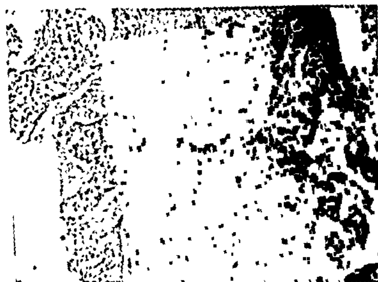


Fig. 1 Peliosis hepatis. Ne... ...e. Unusual incident of asymptomatic hepatomegaly ...o post biopsy complications (H & E, X80)

(3) *Bile Peritonitis* This complication together with hemorrhage constitute almost all of the causes of death from needle biopsy Four cases from Zamcheck's series of 20,016 needle biopsies died as the result of bile peritonitis Unlike postbiopsy hemorrhage, bile peritonitis usually requires immediate attention Bile peritonitis is invariably the consequence of performing a needle biopsy of the liver in patients with chronic obstructive jaundice or perforation of the gallbladder In a fatal case, bile emboli in the lungs were demonstrated at necropsy in a patient with jaundice but without hepatic disease who had been biopsied[*]

(4) *Pneumothorax* This complication has been reported in a few instances but has not been serious[39,47]

(5) *Shock* This complication occurs infrequently, usually following the intercostal route[33,56,57] Originally called "pleural shock," it has been noted in 8 out of 145 consecutive needle biopsies However, re-evaluation of the incidence of shock in nearly

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FIG. 4. Peliosis hepatis. Needle bi… unusual incident of asymptomatic hepatomegaly. No postbiopsy complications. (H & E, X80)

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600 needle biopsies disclosed its presence to be more uncommon and apparently related to the technique and experience of the operator. This "vagotonic" or "pleural" shock is characterized by hypotension, absence of tachycardia, and local or referred pain and persists from one to two hours after biopsy. It has not required any treatment beyond the use of sedatives or analgesics

(6) *Penetration or Biopsy of Extrahepatic Tissue.* Penetration, perforation and biopsy of subcutaneous fat, skeletal muscle, connective tissue, normal and diseased lung, gallbladder, colon, pancreas, right kidney and neoplasms have been reported as complications of needle biopsy of the liver [8,12,22,23,28,30,79,99,100,103,125] These inadvertant complications may result in hemoperitoneum, bile peritonitis, pneumoperitoneum, local hematoma peritonitis and transplantation of neoplastic cells.

DIAGNOSTIC INDICATIONS, ADVANTAGES OF NEEDLE BIOPSY OF THE LIVER

The acceptance of a diagnostic method, such as needle biopsy of the liver, testifies to its value as a reliable procedure in obtaining. (1) an early diagnosis and instituting correct medical and surgical treatment; (2) histological information in order to more satisfactorily follow and treat the course of subacute and chronic hepatic diseases, and (3) the identification of primary neoplastic or metastatic disease of the liver, thereby eliminating an unnecessary surgical operation, a presumptive diagnosis and nonspecific therapeutic management Needle biopsy of the liver has been recognized as the most accurate diagnostic method of liver disease In Schiff's series of 574 biopsies, needle biopsy was useful in 71.8 per cent (it confirmed the diagnosis in 49 8 per cent, corrected the clinical diagnosis in 19 6 per cent, demonstrated unsuspected hepatic disease in 2 4 per cent) and was invaluable in 28 2 per cent In the hands of most investigators needle biopsy of the liver will correct a clinical diagnosis based upon history, physical findings and hepatic function tests in approximately 25 per cent of cases. On the other hand, the indiscriminate use of needle biopsy of the liver is deplored because data obtained by this method and from hepatic function tests may afford only supplementary diagnostic information (Table II).

TABLE II

CORRELATION OF CLINICAL DIAGNOSIS OF CIRRHOSIS OR INDETERMINATE HEPATOMEGALY AND HEPATIC HISTOLOGIC DIAGNOSIS OF CIRRHOSIS AS THE RESULT OF NEEDLE BIOPSY OF THE LIVER IN 426 CASES

Clinical Diagnosis	*Hepatic Histologic Diagnosis*
(1) Indeterminate hepatomegaly (162 cases)	Fatty infiltration—33 Normal—29 Metastatic neoplasm—18 Portal cirrhosis—15 Chronic pericholangitis—11 Chronic passive congestion—8 Granulomatous hepatitis—7 Amyloidosis—4 Hepatitis—4 Florid cirrhosis—5 Sarcoidosis—2 Hemochromatosis—2 Hepatoma—2 Cholangioma—1 Hemosiderosis—1 Pelanis hepatitis—1 Gaucher's disease—1
(2) Portal cirrhosis (136 cases)	Non fatty portal cirrhosis—59 Fatty portal cirrhosis—43 Fatty infiltration—17 Normal—9 Metastatic neoplasm—3 Hepatoma—5 Chronic hepatitis—5 Cirrhosis and hepatitis—2 Cholangioma—1 Cirrhosis and Tuberculosis—1
(3) Hemochromatosis (20 cases)	Hemochromatosis—13 Cirrhosis—7
(4) Hepatolenticular degeneration (3 cases)	Cirrhosis—2 Normal—1
(5) Chronic jaundice (a) Primary biliary or cholangiolitic hepatitis (28 cases)	Chronic pericholangitis with bile stasis 12 Chronic pericholangitis—6 Chronic pericholangitis with bile stasis and cirrhosis—5 Metastatic neoplasm—4 Normal—1
(b) Obstructive jaundice (13 cases)	Bile stasis—4 Cirrhosis and bile stasis—[illegible] Metastatic neoplasm—5 Chlorpromazine hepatitis—7*
(c) Secondary biliary cirrhosis (8 cases)	Cirrhosis and bile stasis—4 Hepatitis—3 Metastatic neoplasm—1
(d) Postnecrotic cirrhosis (26 cases)	Hepatitis and bile stasis—9 Cirrhosis and hepatitis—9 Chronic pericholangitis with bile stasis—2 Chronic pericholangitis—1 Cirrhosis—4 Normal—2
(e) Chronic hepatitis (25 cases)	Hepatitis and chronic pericholangitis—11 Hepatitis, chronic pericholangitis and bile stasis—8 Idiopathic hyperbilirubinemia—2 Normal—3
(f) Constitution hepatic dys function*	Fatty infiltration—1 Normal—3

*Anticipated finding

The indications for and value derived from the use of needle biopsy of the liver are as follows

(1) *Enlargement of the Liver.* Latent portal cirrhosis, subclinical hemochromatosis, amyloidosis, hepatoma, cholangioma, lymphoma, von Gierke's disease, polycystic disease of the liver, sarcoidosis, hepatolenticular degeneration, Gaucher's disease, fungus diseases, fatty liver and parasitic diseases are some pathological conditions producing an enlarged liver in which a definite diagnosis may be obtained by needle biopsy.

(2) *Abnormal Hepatic Function Tests.* Needle biopsy of the liver is indicated in the presence of abnormal values, particularly of the bromsulphalein liver function test, serum bilirubin, zinc sulfate turbidity, serum cholinesterase and serum alkaline phosphatase even in the absence of symptoms and physical findings of liver disease In patients with hepatic dysfunction, the pleurality of functions of the liver, nonspecificity of hepatic function tests and inaccurate correlation of hepatic histological changes with certain clinical and biochemical data in cases of liver disease provide evidence for recommending needle biopsy If this diagnostic criterion is employed, needle biopsy is a means of specifying obscure nonhepatic systemic conditions and confirming presumptive hepatic disease, fatty livers and post-hepatitic sequelae [21, 31, 49, 61, 67, 72, 91, 92, 110, 112]

(3) *Differential Diagnosis of Jaundice.* The value derived from needle biopsy of the liver in determining the diagnosis of jaundice has been emphasized in several reports.[5, 9, 29, 39, 54, 65, 70, 75, 108, 110, 117, 119] It has been recognized, for the most part, that approximately 70 per cent of cases of jaundice can be diagnosed by history and physical findings, and that needle biopsy of the liver corrects an erroneous diagnosis of the type of jaundice in 15 to 20 per cent of cases This technique has been considered hazardous in patients with obstructive jaundice due to lesions in the extrahepatic bile ducts The use of needle biopsy of the liver in jaundiced conditions may prevent an unnecessary abdominal operation and postoperative mortality, particularly in cases of hepatitis It may distinguish histologically between hepatocellular and obstructive jaundice, diagnose acute hepatitis manifesting as obstructive

jaundice, detect intrahepatic neoplastic lesions and contribute to the diagnosis of cases of drug induced obstructive jaundice, constitutional hepatic dysfunction, chronic idiopathic jaundice (Dubin Johnson syndrome), and cholangiolitic hepatitis. A sound rule is to perform a needle biopsy of the liver in patients with jaundice only if warranted after a thorough study of the patient's anamnesis, physical findings, laboratory and hepatic function tests and, occasionally, oral or intravenous cholecystography. In this manner needle biopsy of the liver is safer and more useful as a diagnostic method in jaundice.

(4) *Diagnosis of Neoplasms of the Liver.* It is possible to diagnose approximately 80 per cent of cases with metastatic disease of the liver by needle biopsy.[4,39,57,115] This figure should be anticipated because initially this lesion is located focally with little or no abnormal deviation in the hepatic function tests. Needle biopsy appears more practical in this condition, than a diagnostic, abdominal operation and may secure a more representative specimen of the liver than wedge biopsy.[4,21,45,114] Even when neoplastic disease of the liver is diagnosed clinically, it is advisable to have histological confirmation. Liver biopsy resulted in a correct diagnosis of benign lesions in 16 of 53 patients studied by Schiff in 1951 in whom neoplastic disease of the liver was diagnosed clinically.[87] It has been found advisable to perform multiple biopsies in selected patients in order to demonstrate this condition. Direct biopsy of a hepatic nodule is recommended to differentiate neoplasm from a focal or postnecrotic cirrhosis. Under certain circumstances when malignant neoplasm of the liver is suspected, histological examination of a fresh frozen section of part of the hepatic specimen affords immediate diagnostic evidence.

(5) *Diagnosis and Prognosis of Hepatitis and Fatty Liver.* Serial needle biopsies have been found to be a reliable procedure in diagnosing, treating and following the course and various sequelae of patients with fatty liver or hepatitis which may progress to cirrhosis.[46,47,52,72,73,92,93,98,108,118] Several needle biopsies obtained from patients with primary biliary cirrhosis may demonstrate the evolution of cholangiolitic hepatitis to cholangiolitic

The indications for and value derived from the use of needle biopsy of the liver are as follows:

(1) *Enlargement of the Liver*. Latent portal cirrhosis, subclinical hemochromatosis, amyloidosis, hepatoma, cholangioma, lymphoma, von Gierke's disease, polycystic disease of the liver, sarcoidosis, hepatolenticular degeneration, Gaucher's disease, fungus diseases, fatty liver and parasitic diseases are some pathological conditions producing an enlarged liver in which a definite diagnosis may be obtained by needle biopsy.

(2) *Abnormal Hepatic Function Tests*. Needle biopsy of the liver is indicated in the presence of abnormal values, particularly of the bromsulphalein liver function test, serum bilirubin, zinc sulfate turbidity, serum cholinesterase and serum alkaline phosphatase even in the absence of symptoms and physical findings of liver disease. In patients with hepatic dysfunction, the pleurality of functions of the liver, nonspecificity of hepatic function tests and inaccurate correlation of hepatic histological changes with certain clinical and biochemical data in cases of liver disease provide evidence for recommending needle biopsy. If this diagnostic criterion is employed, needle biopsy is a means of specifying obscure nonhepatic systemic conditions and confirming presumptive hepatic disease, fatty livers and post-hepatitic sequelae.[21, 31,40,61, 67,72, 91,92, 110,112]

(3) *Differential Diagnosis of Jaundice*. The value derived from needle biopsy of the liver in determining the diagnosis of jaundice has been emphasized in several reports.[5, 9,29, 39, 54, 65, 70, 75, 108, 110,117,119] It has been recognized, for the most part, that approximately 70 per cent of cases of jaundice can be diagnosed by history and physical findings, and that needle biopsy of the liver corrects an erroneous diagnosis of the type of jaundice in 15 to 20 per cent of cases. This technique has been considered hazardous in patients with obstructive jaundice due to lesions in the extrahepatic bile ducts. The use of needle biopsy of the liver in jaundiced conditions may prevent an unnecessary abdominal operation and postoperative mortality, particularly in cases of hepatitis. It may distinguish histologically between hepatocellular and obstructive jaundice, diagnose acute hepatitis manifesting as obstructive

[32,38,110,121] While the small caliber of liver tissue procurable by a needle may be insufficient for culture, brucella and tuberculosis have been cultured.

DIAGNOSTIC LIMITATIONS OF NEEDLE BIOPSY OF THE LIVER AS APPLIED TO CIRRHOSIS

To appreciate the diagnostic accuracy of needle biopsy of the liver, one should realize that it is a technique, performed without gross visualization of the surface of the liver, which secures, in the most experienced hands using the Vim Silverman needle, a core of tissue measuring 1 to 3.5 cm. long and 1 to 2 mm wide, which is successfully obtained, at best, 98 per cent of the time Zamcheck has reported that the average biopsy specimen contains 5 to 20 lobules, which is a sufficient sample for recognizing a generalized anatomic change[124] This is true in diseases of the liver only if the lesion is diffuse rather than local The rate of accuracy is no higher when suction biopsies are performed, but the specimen obtained is slightly larger

With this in mind, there are certain technical and clinical limitations of needle biopsy of the liver encountered particularly in cases of cirrhosis.

(1) *Adequacy of Specimen.* Failure to obtain any tissue or an insufficient amount of tissue has been reported in from 1 to 20 per cent of attempted biopsies[8,11,14,38,50,60,88,87,97,108,110,114] It may be particularly difficult to obtain an adequate biopsy from a hard, fibrotic liver in a patient with cirrhosis or from an atrophic, postnecrotic cirrhotic liver.

(2) *Diagnostic Validity of Specimen.* That nodular regeneration must be demonstrated to diagnose cirrhosis morphologically is contended by most investigators Braunstein performed 18 needle biopsies from different areas in each of 30 livers at necropsy demonstrating gross cirrhosis[7] The histological diagnosis of nutritional (portal) cirrhosis was possible in every sample among 221 procured in 13 cases In 10 instances of 507 adequate samples a histological diagnosis was not possible These were 5 biopsies of 152 specimens obtained from post-hepatitic cirrhosis and 5 cases of 131 from postnecrotic cirrhosis Most reports confirm that portal cirrhosis can be diagnosed histologically by

cirrhosis In this manner infectious hepatitis has been recognized to evolve into postnecrotic cirrhosis and hepatoma

(6) *Diagnosis of Hemochromatosis.* The only reliable diagnostic technique to confirm the diagnosis of hemochromatosis is needle biopsy of the liver [43]

(7) *Diagnosis of Amyloidosis.* Hepatic amyloidosis may be primary or secondary, or associated with multiple myeloma or it may be focal. This condition may simulate cirrhosis or hepatic neoplasm clinically [41,75,110]

(8) *Differential Diagnosis of Portal Hypertension* The importance of ascertaining the morphological status of the liver in the diagnosis and surgical treatment of portal hypertension has been emphasized in several reports.[53] In this manner the differentiation between intrahepatic and extrahepatic block of the portal vein may be accomplished, even before advocating the type of shunt, porto-caval, splenorenal or splenectomy This is particularly important in the proper selection of the shunt and the differentiation between primary and secondary hypersplenism.

(9) *Diagnosis of Sarcoidosis, Tuberculosis and Other Granulomatous Diseases* Granulomatous hepatitis or miliary granuloma of the liver may be observed histologically in cases of sarcoidosis, brucellosis, histoplasmosis, erythema nodosum, syphilis, tularemia, lymphoma, actinomycosis and may be a nonspecific finding [7 10 17 28,39 63 81 85 103,109 124] If sufficient hepatic tissue is obtained, the follicles of sarcoidosis may be demonstrated grossly and histologically.[104] Mather and his associates performed needle biopsy of the liver employing the suction technique in 93 patients with sarcoidosis [63] They were able to demonstrate epithelioid-cell follicles in 59 (63 per cent) of these cases and point out that this incidence is similar to that reported in necropsy reports It is possible to diagnose miliary tuberculosis by needle biopsy and obtain positive cultures from the specimen [12 23,39 81 84]

(10) *Persistent Fever of Unknown Origin.* Histological examination of specimen of liver granulomata has been reported to aid is the diagnosis of lymphoma, parasitic diseases, fungus diseases, periarterites nodosa, lupus erythematosus metastatic disease of the liver and leukemia, for example, which cause fever.[30]

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hepatic hemorrhage, inflammation and necrosis. Artifacts may show more fibrosis reflecting subcapsular tissue.[33,39,60,62,124] Finally, it is possible that focal cirrhosis or focal hepatic lesions located in a cirrhotic liver such as a hepatoma or cholangioma may not be identified by needle biopsy.

(3) *Hemochromatosis and Portal Cirrhosis With Hemosiderosis.* Unusual cases of portal cirrhosis with hepatic hemosiderosis may be easily confused histologically with hemochromatosis. This problem arose in one of our alcoholic patients who had several esophageal hemorrhages from varices and had 25 transfusions of blood without clinical findings of hemochromatosis. Histopathologically, small amounts of hemosiderin in the liver and spleen, absence of hemosiderin in the chief cells of the stomach, pancreas, heart and all endocrine glands, a normal pancreas and absence of viscerol discoloration suggested portal cirrhosis and transfusional hemosiderosis.

(4) *Cirrhosis in Infants and Children.* Because the co-operation of the patient is required in order to perform a needle biopsy of the liver, a surgical biopsy may be the preferred technique in infants and children. When the liver is huge in infants and children, a transabdominal route may be performed under intravenous or rectal sodium pentothal anesthesia.

(5) *Cirrhosis With Ascites or Hypersplenism.* These two complications of cirrhosis may indicate that it is too hazardous to perform a needle biopsy of the liver. However, in patients with hypersplenism, despite the danger of intra abdominal hemorrhage, needle biopsy of the liver may be necessary to verify cirrhosis, to differentiate between the intrahepatic and extrahepatic types of portal hypertension and to select properly the type of shunt. Also the extensive intra-abdominal collateral venous circulation may be perforated by needle biopsy leading to hemorrhage. Finally, hypoprothrombinemia observed in patients with cirrhosis may contraindicate needle biopsy of the liver.

(6) *Correlation With Clinical and Laboratory Findings and Therapy.* A limiting feature of needle biopsy of the liver has been reported to be the failure to correlate reliably the histopathological findings with the clinical and biochemical features of cirrhosis

needle biopsy providing an adequate amount of tissue is present. In some instances repeated biopsy of the liver has been necessary to confirm portal cirrhosis Because of the size and variability of the regenerative nodules, measuring from 2 cm to more than 5 cm. in diameter, in postnecrotic cirrhosis an amount of tissue is usually obtained by needle biopsy inadequate to diagnose this condition. Instead, needle biopsies may disclose normal hepatic cells, *focal necrosis, stroma and infiltration of leukocytes*, which is insufficient histological evidence of postnecrotic cirrhosis Postnecrotic cirrhosis, frequently present in patients with hepatolenticular degeneration, may not be confirmed histologically by needle biopsy The histological differential diagnosis between primary and secondary biliary cirrhosis, and between cholangiolitic hepatitis with features of obstructive jaundice, iatrogenic or extrahepatic obstructive jaundice, is difficult and frequently unreliable even in the hands of experienced pathologists.[1,16,21,36,39,41,48,50,56-58,64,70,75,77,80,90,94,117,118,124] As a result of the histological similarities in these conditions and of the potential hazard of bile peritonitis in cases of chronic obstructive jaundice, information derived from history, physical examination and hepatic function tests is relied upon initially in the differential diagnosis of jaundice. The evolution of cholangiolitic (primary biliary) cirrhosis from cholangiolitic hepatitis has been demonstrated morphologically, but diagnosis of the latter condition initially has functional rather than histological implications[118] Usually, the histological differentiation between conditions producing an acute episode of jaundice is more reliable than that in chronic cases where roentgenological or surgical evidence of patency of the extrahepatic bile ducts is necessary. Comparisons between specimens of liver obtained by percutaneous needle biopsy, surgical wedge biopsy or at peritoneoscopy have disclosed not only the advantage of gross inspection of the surface of the cirrhotic liver in the case of the latter techniques, but the possibility of obtaining larger samples than by needle biopsy[4,84,121] On the other hand, needle biopsy is a more simple and practical technique in which better representative samples may be obtained deeper in the liver. In addition, surgical operations may induce

hepatic hemorrhage, inflammation and necrosis. Artifacts may show more fibrosis reflecting subcapsular tissue[25,59,60,82,120] Finally, it is possible that focal cirrhosis or focal hepatic lesions located in a cirrhotic liver such as a hepatoma or cholangioma may not be identified by needle biopsy.

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(6) *Correlation With Clinical and Laboratory Findings and Therapy.* A limiting feature of needle biopsy of the liver has been reported to be the failure to correlate reliably the histopathological findings with the clinical and biochemical features of cirrhosis

[13,14,20 20,34 37,39 42,66 69,71,72,88 91 110 113] The extent of hepatic cell necrosis has been demonstrated to correlate more specifically with jaundice and abnormal levels of serum albumin and globulin and the flocculation tests, than with fibrosis, fatty infiltration or inflammation features in cirrhosis.[113] The activity of cirrhosis may be best assessed by the histological evidence of hepatocellular damage, whereas fibrosis reflects a chronic irreversible pathological process[86] Histological reversal of fatty infiltration in the cirrhotic liver has been considered a less reliable guide in evaluating activity in cirrhosis[111 113] It has also been recognized that the histological findings generally have little prognostic significance

It is best to regard needle biopsy generally as the best single, available diagnostic method in diseases of the liver including cirrhosis Its diagnostic and practical value far exceed its limitations and potential risk. This technique should always be regarded as a valuable, supplementary diagnostic tool, rather than a substitute for clinical judgment.

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Chapter 5

CLASSIFICATION OF CIRRHOSIS

INTRODUCTION

RENE THEOPHILE Hyacinthe Laennec proposed the term "cirrhosis" in 1826 rather than "the common tubercle" because the regenerative nodules present in this condition were "of fawn or yellowish russet, bordering on the greenish."[4,7,29,31,42] Laennec remarked that "this type of growth belongs to the group of those which are confused under the same name of Scirrhus. I believe we ought to designate it with the name of cirrhosis because of its color." The term cirrhosis is derived from the Greek word, kirrhos," denoting "orange colored." In 1905, A. O. J. Kelley remarked that "the term, cirrhosis, has by a vicious transference of meaning become almost inseparable form, with some writers practically identical with the sclerotic process; and indeed by the ill-informed, its meaning is not infrequently expanded so as to include sclerotic and fibrotic processes in other organs."[24] This unitary morphological concept of cirrhosis has never been accepted generally because there are distinctive clinical and pathological features in different types of cirrhosis, particularly in advanced stage of development. Fiessinger postulated that there *exists only one cirrhosis (il n'y a qu'une cirrhose).[11,12] The term* "Laennec's cirrhosis" was employed descriptively in a loose manner. Much discrepancy existed in various classifications of cirrhosis by combining an etiological and pathological nomenclature. Etiologic classifications of cirrhosis included questionable pathogenetic factors such as malarial, syphilitic, streptococcal or parasitic. Until recently, there were individual classifications of cirrhosis proposed in which the definition of cirrhosis was either controversial or unfounded.

EVOLUTION OF CLASSIFICATIONS

In 1911, Mallory defined cirrhosis as a chronic progressive destructive lesion of the liver associated with reparative activity and contraction on the part of the connective tissue.[43] He classi-

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125 ZELMAN, S, Implantation Metastasis after Needle Biopsy of Liver Tumor, JAMA, 165 682 1957.

of cirrhosis based on 550 cases observed at the Boston City Hospital between 1897 and 1931.[43] His classification included (1) obstructive cirrhosis, (2) colon bacillus cirrhosis, (3) healed acute yellow atrophy; (4) streptococcus cirrhosis (infantile), (5) syphilitic cirrhosis, congenital or acquired, (6) pigment cirrhosis; and (7) alcoholic cirrhosis. In 1936, Albot proposed a comprehensive classification of cirrhosis.[2] By 1940, nodular regeneration and fibrosis were emphasized as equally significant pathological features in a textbook on pathological anatomy by MacCallum.[31,32]

A classic publication dealing with the morphology and pathogenesis of cirrhosis was compiled in 1943 by Karsner. He incorporated some of the conceptions of such predecessors as de Josselin de Jong and Moon and considered fibrosis as the pertinent pathological feature of cirrhosis. He also proposed another general classification of cirrhosis (1) Laennec's cirrhosis, (2) fatty cirrhosis (3) pigmentary cirrhosis, (4) biliary cirrhosis; (5) postnecrotic cirrhosis (toxic), (6) congestive cirrhosis ("cardiac"), (7) syphilitic nodular cirrhosis (8) zooparasitic cirrhosis, (9) tuberculosis cirrhosis, and (10) cirrhosis of the lipondoses. He disbelieved that cirrhosis represented a chronic infectious process and, therefore, did not consider so-called infectious cirrhosis or juvenile cirrhosis Karsner also questioned the validity of congestive, syphilitic, tuberculous or postnecrotic cirrhosis and cirrhosis associated with schistosomasis. He suggested that an ideal classification of cirrhosis would be etiological, but must await identification of the causes A category, on the other hand, solely with either etiological, clinical or morphological implications would be confusing and even premature MacMahon and Mallory in 1931 postulated infectious cirrhosis or streptococcal cirrhosis as a specific etiological type of cirrhosis.[46,39]

In 1951, the Registry of Hepatic Pathology of the Armed Forces Institute of Pathology recorded histopathological criteria for hepatic diseases and cirrhosis particularly with reference to the histological findings obtained by needle biopsy of the liver

A Cirrhosis

1 Portal

fied cirrhosis of the liver into five different types. (1) toxic cirrhosis; (2) infectious cirrhosis, (3) pigment cirrhosis, (4) syphilitic cirrhosis, either congenital or acquired, and (5) alcoholic cirrhosis Mallory emphasized "sclerosis" or increased amount of connective tissue in his definition of cirrhosis Kaufman remarked that atrophic cirrhosis "depends on a marked connective tissue development with destruction of considerable liver tissue."[21] He considered that the presence of regenerative nodules was not an indispensable pathological feature of the cirrhotic liver. Kretz in 1905, Rossle in 1930, de Josselin de Jong in 1931, and Eppinger in 1937 were among the first to propose that the morphological constituents of cirrhosis were nodular regeneration, fibrosis, and hepatocellular necrosis.[9,10,27,59] At the first conference of the International Society for Geographic Pathology held at Geneva, Switzerland in 1931, a pathological definition of cirrhosis was considered based on the experience of 65 experts representing 20 European and 8 other nations De Josselin de Jong emphasized at this seminar that a pathological triad was essential in defining cirrhosis (1) proliferation of connective tissue, interstitial, diffuse or reticular, (2) degeneration and necrosis of hepatic cells, and (3) regeneration of hepatic cells He noted also other common pathological features which were variable in extent and intensity, namely (1) particular degenerations, for example, hyalinization, steatosis, necrosis, dissociation, and deposits of pigment, (2) cellular infiltration such as round cells, (3) thickening and proliferation of reticulum, (4) formation of pseudo-biliary ducts or proliferation of interlobular ducts, (5) sclerosis, necrosis and regeneration of blood vessels, and (6) enlargement or atrophy of the liver[9] De Josselin de Jong excluded from the nomenclature of cirrhosis, such conditions as actinomycosis, lymphogranulomas, tuberculosis, cicatrization of abscesses, parasitic lesions and gummata[19,20]

/Moon in 1932 considered cirrhosis to occur in several varieties as a "progressive chronic inflammation, diffuse in extent, accompanied by fibrosis, retrogressive changes in the parenchyma cells and proliferation of remaining cells in the direction of regeneration."[51,52] That same year, Mallory distinguished different types

in the centrolobular sinusoids. In late stages, biliary cirrhosis may become indistinguishable from portal cirrhosis.

4. Those cases of cirrhosis showing pseudolobule formation but which do not fulfill the criteria for any of the three types outlined above are designated as "cirrhosis, type undetermined."

B. The designation "portal fibrosis, etiology undetermined," is used for those cases in which there is a rather marked increase in the amount of portal collagenous tissue and sometimes in the number of small bile ducts, but in which pseudolobule formation is not convincingly demonstrated. It may be that some of these cases represent healed biliary cirrhosis but it is also possible that they represent a stage in the pathogenesis of cirrhosis. Until this fact is established, however, it is believed that the term "early cirrhosis" is best avoided.

C. Whether or not fatty metamorphosis represents a stage in the pathogenesis of all cases of cirrhosis is uncertain. For this reason, it is coded as a separate entity.

D. The term active hepatitis is reserved at the Armed Forces Institute of Pathology for those cases which are presumably of viral origin. In addition, they may be designated as slight, moderate, or marked. A recent study, however, has clearly demonstrated that the degree of histopathological changes is not an accurate index of clinical severity since significant alterations are observed even in clinically mild cases. Biopsies which have been performed from 1 to 6 days after the clinical appearance of jaundice in cases of this disease reveal a marked portal inflammation consisting of mononuclear cells sometimes accompanied by a few eosinophilic leukocytes. In addition, there is a diffuse scattering of mononuclear cells throughout the lobules, usually within the sinusoids. Soli-[illegible]
m[illegible]
be[illegible]
likened to the Councilman bodies of yellow fever. The Kupffer cells are prominent and some are distended with a finely granular yellow brown pigment which is believed to be lipochrome derived from necrotic parenchymal cells. The histopathological picture of acute viral hepatitis apparently

2 Postnecrotic
3 Biliary
4 Type undetermined (specify most likely)

B Portal fibrosis, etiology undetermined
C Fatty metamorphosis (specify slight, moderate or marked)
D Active hepatitis
E Toxic hepatitis (specify agent)
F Central necrosis (etiology undetermined or specify agent if known)
G Granulomata or granulamatous hepatitis (etiology undetermined, or specify agent when demonstrated histologically)
H *Bile stasis*, obstructive type (obstructive jaundice)
I Cholangitis or pericholangitis
J Specific disease where the etiologic agent is demonstrated, for example, amoebiasis, tuberculosis, schistosomiasis, etc
K Hemochromatosis
L Hemosiderosis

Criteria

A Cirrhosis

1 Portal cirrhosis An increase in the number of small bile ducts and in the amount of portal collagenous tissue with definite pseudolobular formation For practical purposes, portal cirrhosis is regarded as a diffuse hepatic disease *which involves all of the portal canals in a uniform degree*

2 Postnecrotic cirrhosis Broad areas of scarring, sometimes with an increased number of bile ducts and pseudolobular formation, but also showing one or more portal canals which are either within normal limits or are only slightly altered, and which do not enter into the formation of pseudolobules It is believed that postnecrotic cirrhosis should be employed as a morphological diagnosis only and should not be interpreted as implying a specific etiology Attempts to differentiate between portal and postnecrotic cirrhosis *by means of liver biopsy are uncertain* and a high degree of accuracy should not be anticipated.

3 Biliary Cirrhosis: An increase in the amount of the portal collagenous tissue and in the number of small bile ducts, sometimes with pseudolobule formation, but usually with a centrally located efferent vein and small bile "thrombi"

hemochromatosis, however, a rare simultaneous occurrence of portal cirrhosis and hemosiderosis has been considered

K. Hemosiderosis of the liver is not infrequently encountered in the wake of multiple transfusions, but it is ordinarily not followed by cirrhosis A cirrhotic liver may, however, retain hemosiderin pigment.

A comprehensive and contempory classification of cirrhosis was proposed by Watson in 1952.[6] He distinguished between two main types of cirrhosis, one in which a fatty liver is the main pathogenetic feature, and another in which cirrhosis is non fatty during its morphogenesis The production of cirrhosis from fatty livers by various deficient diets in experimental animals and the studies of serial needle biopsies of the fatty liver in humans formed the basis of this classification

Watson's Classification of Cirrhosis

I Primarily fatty in pathogenesis
  A. Dietary deficiency (kwashiorkor)
  B Chronic alcoholism and dietary deficiency—Laennec type
  C. Toxic fatty liver (arsenic, CCl_4, phosphorus, certain systemic infections)
  D Diabetic fatty liver
II. Primarily non fatty in pathogenesis
  A Viral or idiopathic
    1 Postnecrotic (toxic or coarsely nodular, healed acute atrophy)
    2 Diffuse portal (chronic hepatitis with fibrosis, mainly portal)
      a With hepatocellular impairment
      b Cholangiolitic (primary biliary; Hanot)
    3 Transitions and mixtures
  B Parasitic schistosomiasis
  C Syphilitic—probably only hepar lobatum
  D. Brucellosis (?)
  E Obstructive biliary (cholestatic and cholangitic)
  F Metabolic error
    1 Hemochromatosis ("pigmentary" cirrhosis)
    2. Wilson's disease]
    ] amino-aciduria
    3 Fanconi's syndrome]

changes rather rapidly and, within 2 to 3 weeks, the portal and diffuse mononuclear cell reaction resolves except for small aggregates which persist and which may represent foci of necrosis Pigmented Kupffer cells usually remain and may be quite prominent Morphological changes characteristic of "chronic viral hepatitis" have not been ascertained with certainty

E. The term "toxic hepatitis" is reserved for those cases which show a relatively aseptic necrosis of the centrolobular liver cells with very little associated inflammatory reaction Pigmented macrophages in this area are usually prominent The histological hepatic changes seen in carbon tetrachloride poisoning are a good example of this type of hepatitis

F Central necrosis of liver necrosis of liver cells about efferent veins as seen in hypoxemic condition, usually accompanied by infiltrations of polymorphonuclear leukocytes.

G Granulomata or granulomatous hepatitis Self-explanatory, usually but not necessarily confined to portal areas, varied etiology

H Bile stasis obstructive type Small bile thrombi within the sinusoids around the central efferent vein, without evidence of inflammation in the portal canals or in the lobules

I Cholangitis or pericholangitis is reserved for those cases which show an inflammatory reaction confined to the portal canals, with little or no inflammation in other parts of the lobules and with bile stasis of the obstructive type

The terms "cholangiolitis" and "cholangiolitic hepatitis" have not been used at the Armed Forces Institute of Pathology since the histopathological criteria necessary for their diagnoses are not well understood Suspected cases have shown changes which are consistent with those seen in cases of prolonged viral hepatitis

J. Hemochromatosis is characterized by cirrhosis of the liver of the portal type and deposition of abundant hemosiderin and hemofuchin pigments in liver cells, Kupffer cells, epithelial cells of bile ducts and phagocytic cells of the stroma The cause of this disease is not known The condition is probably not a primary liver disease as many other organs are involved in this process The combination of portal cirrhosis in the presence of the pigments is usually indicative of

severity. The entity includes several varieties, each having its own pathological and clinical characteristics

II *Classification* The classification should be morphologic, etiologic and functional

A Morphologic:

1 Portal (an unsatisfactory term, but no more appropriate name was found) (Popper proposed the term septal for this type of cirrhosis)

2 Postnecrotic

3 Biliary with obstruction of the extrahepatic biliary tract without obstruction of the extrahepatic biliary tract

It is realized that the same liver may show features of more than one type This may make classification difficult in some instances

B Etiologic Factors accepted by all members were:

1 Malnutrition

2 Ethyl alcohol (the exact mechanism of cirrhosis production is unknown)

3 Viral hepatitis

4 Obstruction of the extrahepatic biliary tract

5 Cardiac failure

6 Hemochromatosis

7 Congenital syphilis (rarely)

The etiological role of the following factors has been considered and now awaits further assessment:

1 Toxic agents, such as carbon tetrachloride, trinitrotoluene

2 Granulomatous lesions occurring in such conditions as brucellosis, tuberculosis and sarcoidosis

3 Helminthic infestations such as schistosomiasis

4 Disturbances in copper metabolism

There are some instances of cirrhosis in which the etiology is at present obscure

The etiology of biliary cirrhosis without obstruction of extrahepatic biliary tract is also not yet established

C Functional

1 Liver cell failure, shown by clinical and laboratory data, such as

a Jaundice

b Ascites

4 Porphyria hepatica

G. Cardiac (central necrosis and fibrosis resulting from long standing chronic passive congestion)

Spellberg recently proposed a classification of cirrhosis similar to that employed in the nomenclature of diseases of the heart.[64] This included (1) anatomical diagnosis; (2) etiological diagnosis; and (3) functional impairment. The latter category was divided into three groups. Group 1—minor alterations of hepatic function tests without subjective symptoms, group 2—moderate alterations of hepatic functions together with minor symptoms of cirrhosis such as anorexia, fatigue, and dyspepsia; and group 3—marked alterations of hepatic function tests and clinical evidence of ascites or portal hypertension. This new classification is useful in that it introduces reversible functional and therapeutic components of cirrhosis in living patients and also necessitates histological diagnosis usually by needle biopsy of the liver

In 1956, during the Fifth Panamerican Congress of Gastroenterology held in Havana, Cuba, a similar classification and *nomenclature of cirrhosis* was *proposed* by a group of outstanding authorities in the field of hepatic disease as follows in outline form.[15]

Fifth Panamerican Congress of Gastroenterology: Report of the Board for Classification and Nomenclature of Cirrhosis of the Liver

I *Concept of Liver Cirrhosis.* The definition of cirrhosis is essentially anatomic with an additional clinical concept

A. Anatomic definition

1 All parts of the liver are involved without necessarily affecting each lobule

2 Cellular necrosis is present at some stage of the disease

3. Nodular parenchymal regeneration

4 Diffuse fibrosis

5. Disorganization of the lobular architecture with connective tissue bands uniting centro-lobular zones with the portal tracts

B Clinical concept includes.

1. Chronic disease

2 Liver cell failure and portal hypertension of variable

Fatty cirrhosis
Bronzed diabetes
Pigmentary cirrhosis
Parasitic cirrhosis
Neoplastic cirrhosis
Hypersplenomegalic cirrhosis
Cirrhosis of the Banti syndrome
Cirrhosis of the Fanconi syndrome
Hanot's cirrhosis
Tuberculous cirrhosis
Malarial cirrhosis
Toxic cirrhosis
Alcoholic cirrhosis
Post hepatic cirrhosis

The latter two terms are excluded not because the Board disagrees with ethyl alcohol or viral hepatitis as etiologic factors but because they believe cirrhosis should be classified morphologically, etiologically and functionally

Fibrosis means increase of connective tissue and should only have this connotation The site of the fibrosis should be specified Fibrosis should not be used synonymously for cirrhosis

IV *Post necrotic Cirrhosis* This is a true cirrhosis characterized by irregular distribution of the lesions in the liver with areas of preserved architecture Frequently there are broad bands of fibrous tissue which follow collapse of the parenchyma It must be distinguished from *post necrotic scarring* (e g following healed abscesses or gumma), in which the surrounding parenchyma is normal

Zonal fibrosis (usually portal) may also follow viral hepatitis without the lesion fulfilling the definition of cirrhosis stated in number I

V *Sequela of Viral Hepatitis*

Chronic Hepatitis is a condition in which there is continuing portal or focal inflammation without fulfilling characteristics of a true cirrhosis It may be completely reversible or may possibly proceed to a cirrhosis but more documentation is needed to confirm this Clinical manifestations may be minimal Flocculation and bromsulphalein tests are frequently abnormal

Both *portal* and *postnecrotic cirrhosis* can follow viral hepatitis

c Pre-coma and coma
d Low-serum albumin level
e Prothrombin deficiency not corrected by administration of vitamin K
2 Portal hypertension is shown by
a Splenomegaly
b Esophageal varices
c Demonstration of a raised portal pressure by the newer techniques now available
3 Activity of the disease, whether progressing, regressing or stationary

The *Board believes that a functional classification should be attempted* in spite of the many difficulties in evaluating liver cell failure, for instance, jaundice may be due not only to liver failure since hemolysis and bile duct obstruction may contribute Ascites is also not due only to liver cell failure An extensive collateral circulation contributes to the production of coma Grading of the functional state is also desirable but must await further discussion

Needle biopsy of the liver is useful in establishing the morphological diagnosis and in assessing the degree of activity of the process

In the following examples, the practical application of this criteria for the classification of liver cirrhosis is demonstrated

1 Portal cirrhosis with alcoholism, liver cell failure and *without portal hypertension, progressing*
2 *Post-necrotic cirrhosis, following viral hepatitis, without liver cell failure* and with *portal hypertension, regressing*
3 *Biliary cirrhosis* after *stricture of common bile duct,* without liver cell failure and without *portal hypertension,* progressing

III *Meaning of Terms* The following should be abolished as useless or leading to confusion:

Pseudocirrhosis
Monolobular cirrhosis
Perilobular cirrhosis
Atrophic cirrhosis
Hypertrophic cirrhosis
Capsular cirrhosis

Until the etiology of cirrhosis can be established without question and hepatic function tests employed as a more reliable functional therapeutic guide, it may be temporarily feasible to arrange separate clinical, pathological, and histological classifications of cirrhosis, the latter due to diminutive needle biopsies. For example, when hepatolenticular degeneration is the clinical diagnosis, postnecrotic cirrhosis usually is the gross morphological diagnosis, and portal or postnecrotic cirrhosis the histological diagnosis. This is true, also, when primary biliary cirrhosis is a clinical diagnosis, and biliary cirrhosis or chronic pericholangitis the gross morphological or histological diagnosis (Table I).

An attempt is made, therefore, to separate clinical, gross morphological, and histopathological nomenclature of cirrhosis.

A. Clinical Classifications of Cirrhosis of the Liver

(1) *Portal Cirrhosis.* This type of cirrhosis of the liver is considered commonly to be the consequence of malnutrition, especially protein deficiency and viral hepatitis.[28,29,32,33,45-50,55,56] Actually, it is often cryptogenic. The early stage of portal cirrhosis is characterized by such nondescript symptoms as flatulent indigestion, morning nausea, vomiting, fatigue, weakness, anorexia, and sexual impotence. The physical findings suggestive of portal cirrhosis are ascites, abdominal distention, malnutrition, loss of weight, feminizing features, jaundice, gastrointestinal hemorrhage, spider angioma, palmar erythema, hepatosplenomegaly, pedal edema, collateral venous circulation and esophageal varices. When jaundice is associated with portal cirrhosis, it represents either transient or terminal hepatic insufficiency. Repeated bouts of refractory ascites are observed in portal cirrhosis in contrast to many other types of cirrhosis. Death usually results from an exsanguinating esophageal hemorrhage, hepatic coma, or intercurrent infection, often contributed to by secondary hypersplenism. The common laboratory findings in portal cirrhosis are retention of bromsulfathalein dye, hypoalbuminemia, hyperglobulinemia, positive hepatic flocculation tests, leukocytosis, abnormal plasma prothrombin values, and esophageal varices visualized by esophagoscopy and roentgenogram (Table I).

Cholangiolitic biliary cirrhosis possibly follows viral hepatitis but further evidence is needed to convince the Board

This classification of cirrhosis appears ideal and practical. *However, the etiological factor in most cases of cirrhosis in humans* is presumptive and, actually, only protein malnutrition, viral hepatitis, hepatotoxic chemicals, and biliary obstruction are proven and unquestioned pathogenetic factors. In fact, the etiological factor is purely speculative in most cirrhotic conditions. Secondly, the Board appreciated that to construct a functional classification of cirrhosis is difficult because discrepancies may exist between the morphological, biochemical, and clinical features of cirrhosis, It is perhaps improbable at the present time that a diseased condition of the liver with plurality of dysfunctions can be satisfactorily classified in a manner similar to cardiac disease. The current hepatic function tests are too nonspecific and, unlike other intrinsic functional tests, not quantitative to act as an accurate standard index. Until more information is secured about the etiology of cirrhosis and measurable biochemical functions of the liver, this classification may be too premature This, however, should not deter from its usefulness as a functional-therapeutic gauge which may be employed advantageously by the clinician and surgeon. Along this line Schaffner, Popper, and Dalla Torre in 1956 also proposed their functional-therapeutic classification of cirrhosis based on morphological criteria of the progression of the desease, the architecture of the regenerative nodules, porto-hepatic vascular anastomoses, and the amount of hepatocellular damage.[61] They correlated hepatocellular degeneration with jaundice, gastrointestinal bleeding, and abnormal hepatic function tests and noted that the only clinical feature that correlated with advanced cirrhosis was splenomegaly Hepatic function tests were too insensitive to indicate the extent of cirrhosis Progression of cirrhosis, however, was observed frequently when the patient disclosed jaundice, ascites, splenomegaly, spider angioma, palmar erythema and increased values of the serum gamma globulin and thymol turbidity. In evaluating prognosis and therapy of cirrhosis, these findings offered an important grade for the clinician

tracted course of portal cirrhosis, patients with postnecrotic cirrhosis tend to have a progressively deteriorating downward clinical course measured in months to several years. Marked hypergammaglobulinemia, leukopenia, positive hepatic flocculation values, low plasma cholesterol ester and cholinesterase values, thrombocytopenia, increased values of the direct and indirect serum bilirubin, serum transaminase and iron and hypoprothrombinemia are pertinent laboratory findings.

(3) *Biliary Cirrhosis*

(a) *Primary Biliary Cirrhosis*. This type of cirrhosis is considered synonymous with cholangiolitic cirrhosis and the hypertrophic cirrhosis of Hanot.[illegible] It may be indistinguishable from the condition due to congenital atresia of the intrahepatic bile ducts.[illegible] It may be associated with elevated values of the plasma cholesterol and phospholipids, in which case xanthomatous lesions of the skin may develop.[illegible] The cause of the disease is unknown. The disease usually is confined to middle age in women and runs a prolonged clinical course. Intractable generalized pruritus, abdominal pain, weakness, intolerance to fatty foods, loss of weight, osseous pain, steatorrhea, and menstrual irregularities are common complaints. Cutaneous melanosis, excoriations, jaundice, xanthomata, enlarged liver and spleen, lymphadenopathy, clubbed fingers, low-grade fever, and alopecia are common physical findings. Hepatic insufficiency develops late in the course of the disease. Laboratory studies reveal findings consistent with obstructive jaundice. Eventually the clinical picture resembles portal or postnecrotic cirrhosis. The diagnosis of primary biliary cirrhosis is essentially clinical and must be corroborated radiologically or by surgery in order to exclude obstructive lesions of the extrahepatic biliary system.[illegible]

(b) *Secondary Biliary Cirrhosis*. This type of cirrhosis is produced rarely by prolonged obstruction of the extrahepatic bile duct usually from postoperative biliary stricture, choledocholithiasis, congenital extrahepatic biliary atresia, parasitic infestation, and neoplasm.[illegible] The clinical and laboratory features are similar to those observed in cases of primary biliary cirrhosis. The diagnosis of secondary biliary cirrhosis may be presumptive only

TABLE I
CLASSIFICATION OF CIRRHOSIS OF THE LIVER

Clinical	*Gross Morphological*	*Histological*
1 Portal sequellae of malnutrition, viral hepatitis bacterial or viral infections hepatotoxins endocrinopathy, etc	1 Portal	1 Portal
2 Postnecrotic sequellae of viral hepatitis or hepatotoxins	2 Postnecrotic	2 Postnecrotic (needle biopsy?)
3 (a) 'Primary Biliary' post-hepatitic, cholangiolitic (b) Secondary Biliary extra hepatic, obstructive	3 Biliary	3 Biliary (a) cholangitic (b) acholangitic (c) cholangiolitic
4 Hemochromatosis primary or secondary	4 Hemochromatosis	4 Hemochromatosis
5 Hepatolenticular Degeneration		
6 Cirrhosis in Infants and Children (Etiological Implications)		

(2) *Postnecrotic Cirrhosis.* This type of cirrhosis of the liver may be the sequela of viral hepatitis or hepatotoxic agents [4, 23, 56, 58, 63-66] *It represents presumably vigorous parenchymal regeneration* of a liver following massive hepatic necrosis The clinical picture of postnecrotic cirrhosis is not characteristic and probably cannot be diagnosed adequately without a sufficient hepatic biopsy specimen obtained by needle or peritoneoscope Usually the patient has symptoms more, but not necessarily, indicative of hepatic insufficiency, such as prostration, jaundice, upper abdominal pain, loss of weight, and bleeding tendencies than of portal cirrhosis A palpably irregular, nodular liver, splenomegaly, edema, and fever are the common physical findings Hepatic insufficiency is generally progressive, and hypersplenism and bleeding esophageal varices are common Postnecrotic cirrhosis is more commonly noted in females and often follows the menarche, pregnancy, and menopause. Hepatic coma and hemorrhage from esophageal varices are the usual causes of death Unlike the pro-

(1) *Portal Cirrhosis*: The regenerative nodules in this type of cirrhosis are usually uniform in size and have a diameter of 0.5 cm. or less.[2,14,17,25,72] The nodules are approximate to one another, separated by a narrow zone of fibrous connective tissue. Grossly, the liver of portal cirrhosis has been referred to as granular or hob-nail. On the basis of the weight of the liver, portal cirrhosis may be either atrophic or hypertrophic. Usually the gross livers of portal cirrhosis weigh from 2,000 to 4,500 gm., respectively. The color of the liver of portal cirrhosis varies from different shades of yellow to gray.

(2) *Postnecrotic Cirrhosis*. The regenerative nodules in postnecrotic cirrhosis are large or lobar, or, on the other hand, nodular, measuring 0.5 to 2.0 cm. in diameter.[4,5,8,44] Actually, these irregularly enlarged regenerative nodules are the main pathognomonic feature. Broad zones of fibrous connective tissue separate the regenerative nodules. The liver of postnecrotic cirrhosis is usually atrophic, varying from 500 to 1,200 gm. in size. The color may be yellow, green or brown.

(3) *Biliary Cirrhosis*: Biliary cirrhosis resembles portal cirrhosis grossly, is usually hypertrophic, and is differentiated grossly from portal cirrhosis only by its green discoloration.[33-41,54]

(4) *Hemochromatosis*. This type of cirrhosis similarly resembles portal cirrhosis grossly, is usually hypertrophic, and is differentiated from portal cirrhosis by its red-brown color.[27,42]

C. Histopathological Classification of Cirrhosis

Histologically, cirrhosis of the liver can be divided into four main groups. However, in many cases such a distinction is impossible when an insufficient specimen is obtained by needle biopsy of the liver. To adequately fulfill a histological diagnosis of cirrhosis the following lesions must be present: (a) nodular parenchymal regeneration; (b) increased amounts of fibrous connective tissue in the form of stroma. Degenerative changes or necrosis of the parenchymal cells may be present, and porta-venous anastomoses, invariably and intimately associated with regenerative nodules, may not be observed in the biopsy specimen.

(1) *Portal Cirrhosis*. In this type of cirrhosis there is uni-

after prolonged obstructive jaundice and histological confirmation of hepatic features. Infestations in the bile ducts from Clonorchis sinensis, Fasciola hepatica, and Ascaris lumbricoides may produce the so-called zooparasitic type of biliary cirrhosis. Surgical correction of the extrahepatic obstruction in this type of biliary cirrhosis may induce a reversible clinical state. Otherwise, the disease progresses slowly and simulates the course of portal or postnecrotic cirrhosis.

(4) *Hemochromatosis*. This disease is cryptogenic and nearly always affects males in the fifth or sixth decade of life. Cirrhosis, diabetes mellitus, cutaneous melanosis, and hypogonadism are common clinical features of hemochromatosis. Portal hypertension, hepatic insufficiency, congestive heart failure, ascites and hepatoma may develop eventually. There are two types, primary or the classic type, in which there may be a heredito-familial trait, and secondary hemochromatosis, which is associated with various chronic anemias and especially aplastic anemia.[22]

(5) *Hepatolenticular Degeneration*: This disease occurs in families with a high incidence of consanguinity. There are the hepatic, lenticular and hepatolenticular clinical forms. Clinical manifestations include dementia, extrapyramidal neurologic picture, Kayser-Fleischer corneal rings, and malnutrition. Cirrhosis itself may occur late in the clinical course, except in the hepatic form. Amino-aciduria, hypocupremia, abnormal storage of copper, and minimal to absent evidence of hepatic insufficiency are present usually in this condition. The disease is relentlessly progressive.[71]

(6) *Cirrhosis in Infants and Children*: This broad etiological group includes cirrhoses associated with such conditions as galactosemia, congenital fibrocystic disease of the pancreas, Kwashiorkor, glycogen-storage disease, sickle-cell anemia, veno-occlusive disease, and erythroblastosis fetalis.

B. Gross Morphological Classification of Cirrhosis of the Liver

The gross appearance of the regenerative nodules of the cirrhotic liver and the weight and color of the liver offer valuable information for a gross morphological classification of cirrhosis.

(1) *Portal Cirrhosis:* The regenerative nodules in this type of cirrhosis are usually uniform in size and have a diameter of 0.5 cm. or less.[illegible] The nodules are approximate to one another, separated by a narrow zone of fibrous connective tissue. Grossly, the liver of portal cirrhosis has been referred to as granular or hobnail. On the basis of the weight of the liver, portal cirrhosis may be either atrophic or hypertrophic. Usually the gross livers of portal cirrhosis weigh from 2,000 to 1,500 gm., respectively. The color of the liver of portal cirrhosis varies from different shades of yellow to gray.

(2) *Postnecrotic Cirrhosis.* The regenerative nodules in postnecrotic cirrhosis are large or lobar, or, on the other hand, nodular, measuring 0.5 to 2.0 cm. in diameter.[illegible] *Actually, these irregularly enlarged regenerative nodules are the main pathognomonic feature. Broad zones of fibrous connective tissue separate the regenerative nodules. The liver of postnecrotic cirrhosis is usually atrophic, varying from 500 to 1,200 gm. in size. The color may be yellow, green or brown.*

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(1) *Portal Cirrhosis.* In this type of cirrhosis there is uni-

form alteration of the hepatic architecture.[3,31-33] The hepatic veins are located in various areas of the hepatic nodule. The size of the regenerative nodules is 0.5 cm. or smaller, separated from one another by narrow zones of fibrous connective tissue. The regenerative nodules may be the site of various amounts of fatty infiltration, mild to moderate focal cirrhosis, polymorphonuclear leukocytosis, and infrequent bizarre hepatic cells. Alcoholic-hyalin deposits may be found in the cytoplasm of the hepatic cells in portal cirrhosis. In the internodular stroma are found increased numbers of bile ducts, infiltrations of leukocytes, compressed small venules, and blood vessels typified by the absence of inflammatory changes. The amount of fat in the regenerative nodule determines whether the cirrhosis is fatty.

(2) *Postnecrotic Cirrhosis.* Histologically, this type of cirrhosis is characterized by irregularly shaped regenerative nodules which are usually larger than 1 cm. in diameter, separated by broad bands of fibrous connective tissue. It is in this type of cirrhosis that needle biopsy of the liver offers minimal histological evidence of a cirrhosis only because of the small size of the biopsy (2 mm. x 2 cm.).[23,66] If a larger needle biopsy specimen is procured, the regenerative nodules may be identified. Bizarre hepatic cells, moderate to severe focal necrosis, monocytic infiltration, rarity of fatty infiltration, and absence of alcoholic-hyalin in the hepatic cellular cytoplasm are some histological findings in the regenerative nodules of postnecrotic cirrhosis.[3] The internodular stroma are usually broad and contain collapsed reticular framework, increased amounts of bile ducts, infiltration of monocytes, compressed hepatic veins, and inflammatory changes in the blood vessels.

(3) *Biliary Cirrhosis.* Microscopically, biliary cirrhosis has limited clinical connotation. The histological recognition of biliary cirrhosis depends upon the presence of the usual criteria of portal or postnecrotic cirrhosis in addition to cholestasis. There is no characteristic distinction histologically between primary and secondary biliary cirrhosis regardless of the presence of cutaneous xanthomatosis. In addition, there is a marked proliferation of fibrous connective tissue in the portal spaces together

with abundant infiltrations of lymphocytes. The bile canaliculi, small bile ducts, and portal areas may contain small collections of bile. The hepatic cells may appear normal with the exception of those lying adjacent to the portal area, where necrosis and degeneration of the hepatic cells occurs. Commonly, primary biliary (cholangiolitic) cirrhosis is the histological picture from a needle biopsy of the liver which reveals so-called pericholangitis with bile stasis.[14,67] Acholangitic biliary cirrhosis reflects the absence of intrahepatic bile ducts.

(4) *Hemochromatosis.* This type of cirrhosis has all the histological features of portal cirrhosis in addition to abundant amounts of hemosiderin in the hepatic cells, stroma, bile duct epithelium, and Kupffer cells. Berlin Blue or Prussian Blue stains are employed to stain hemosiderin particles.

The most practical, general (clinical and pathological) classification of cirrhosis appears to include clinical and laboratory information, histological diagnosis obtained by needle biopsy of the liver and, if possible, description of the gross morphological appearence of the liver obtainable by peritoneoscopy, necropsy examination, or during an abdominal operative exploration. In certain instances, such as hepatolenticular degeneration, hemochromatosis, or congenital fibrocystic disease of the pancreas cirrhosis is but one condition of a general disease. Therefore the clinician must decide whether a case of cirrhosis is primary or secondary. It may be found ideal to attempt, if possible, to reconstruct the functional-therapeutic evaluation of cirrhosis. This necessitates objective correlation of serial needle biopsies of the liver with particular attention paid to the degree of hepatocellular degeneration and the results of serial hepatic function tests.

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much greater in the Far East, Asia, Iraq, Africa, Chile, Italy, Switzerland, and is lower in the Scandanavian countries and Russia.[1, 52, 84, 107, 110, 123, 130, 134] Ratnoff and Patek in their classic monograph on Laennec's cirrhosis published in 1942 noted that the incidence of portal cirrhosis based on a study of necropsies was 6.95 per cent in Geneva, Switzerland, 6.3 per cent in Baltimore, Maryland, 5.2 per cent in Vezagapatum, South India, and, on the other hand, 1 per cent in Philadelphia, 0.99 per cent in the Phillipine Islands, and 0.13 per cent in Portland, Oregon.[85] Although little significance can be attached to the factor of race and nationality, portal cirrhosis in this country appears to be more prevalent among the Irish, Italians and Negroes. Stacey has described a cryptogenic portal cirrhosis in Iraq occurring predominently among middle-aged farmers having splenomegaly.[119] The most common cause of death was hepatic insufficiency in contrast to the more rare esophageal hemorrhage. An unusual type of cirrhosis frequent among the underprivileged of Mexico has been reported due to the association of alcoholism, malnutrition, and tuberculosis.[104] It would seem that such statistics emphasize only the incidence of alcoholism and protein deficiency in various sections of the world although a great discrepancy exists between these statistics and clinical observations.[117]

Portal cirrhosis occurs most commonly in the fifth and subsequent decades of life, and in this country is seen more commonly among men. In this series, there were 8 males to 1 female, in the investigations of Boles and Clark, Douglas and Snell, Fleming and Snell, respectively, the ratio was 3 to 1;[11, 33, 42] in other series such as Ratnoff and Patek, Hall, Olsen, and Davis and Kirshbaum and Shure, the ratio has been 2 to 1.[45, 63, 85] The incidence of portal cirrhosis is particularly high among bartenders, tense middle-aged businessmen, traveling salesmen, laborers, mentally diseased persons including character neurotics and unemployed people. In a series of 500 consecutive cases of portal cirrhosis at Charity Hospital in New Orleans, 82 per cent were laborers or unemployed, 74 per cent were men, and 13 per cent were Negroes. The general population of Negroes in this hospital is about 75 per cent, and in Louisiana about 47 per cent.

Chapter 6

PORTAL CIRRHOSIS

INTRODUCTION

PORTAL CIRRHOSIS, the most common type of cirrhosis, is also one of the most prevalent medical conditions encountered in the world. The term, portal cirrhosis, may imply pathological features, and several descriptive terms have been used synonymously as atrophic, hypertrophic, fatty, nodular, multilobular, hobnail, periportal, Laennec's and chronic septal cirrhosis or even interstitial hepatitis or diffuse hepatic fibrosis Etiological terms such as alcoholic, nutritional, cryptogenic, posthepatitic, toxic, beer or gin-drinkers' liver have also been applied to this condition Portal cirrhosis is defined loosely, and its definition varies with different clinicians. This condition actually designates either a clinical syndrome or a particular type of pathological liver in which the salient gross morphological appearance is characterized by small granular, regularly arranged regenerative nodules. Portal cirrhosis, therefore, should never be confused pathologically with chronic hepatitis or hepatic fibrosis It is a useful pathological description of a specific type of cirrhosis and probably, is most commonly attributed to malnutrition or viral hepatitis It is generally accepted that dietary deficiency of protein is the main etiological factor of portal cirrhosis rather than prolonged imbibition of ethyl alcohol The pathological sequence of portal cirrhosis in alcoholic patients has been traced by Connor beginning as a fatty liver [23,24]

INCIDENCE

The incidence of portal cirrhosis varies in different parts of the world or even in the same country. De Josellin de Jong in 1931 compiled information on 585,963 necropsies throughout the world and found the incidence of cirrhosis to be less than 3 per cent in 463,562 and over 3 per cent in 122,401 of these cases, of which over half were cases of portal cirrhosis [30] The incidence is

much greater in the Far East, Asia, Iraq, Africa, Chile, Italy, Switzerland, and is lower in the Scandanavian countries and Russia [1,52,94,107,119,123,130,134] Ratnoff and Patek in their classic monograph on Laennec's cirrhosis published in 1942 noted that the incidence of portal cirrhosis based on a study of necropsies was 6 95 per cent in Geneva, Switzerland, 6 3 per cent in Baltimore, Maryland, 5.2 per cent in Vezagipatum, South India, and, on the other hand, 1 per cent in Philadelphia, 0 99 per cent in the Phillipine Islands, and 0.13 per cent in Portland, Oregon [95] Although little significance can be attached to the factor of race and nationality, portal cirrhosis in this country appears to be more prevalent among the Irish, Italians and Negroes Stacey has described a cryptogenic portal cirrhosis in Iraq occurring predominently among middle-aged farmers having splenomegaly [119] The most common cause of death was hepatic insufficiency in contrast to the more rare esophageal hemorrhage An unusual type of cirrhosis frequent among the underprivileged of Mexico has been reported due to the association of alcoholism, malnutrition, and tuberculosis [104] It would seem that such statistics emphasize only the incidence of alcoholism and protein deficiency in various sections of the world although a great discrepancy exists between these statistics and clinical observations [117]

Portal cirrhosis occurs most commonly in the fifth and subsequent decades of life, and in this country is seen more commonly among men In this series, there were 8 males to 1 female, in the investigations of Boles and Clark, Douglas and Snell, Fleming and Snell, respectively, the ratio was 3 to 1,[14,31,42] in other series such as Ratnoff and Patek, Hall, Olsen, and Davis, and Kirshbaum and Shure, the ratio has been 2 to 1 [44,65,95] The incidence of portal cirrhosis is particularly high among bartenders, tense middle-aged businessmen, traveling salesmen, laborers, mentally diseased persons including character neurotics, and unemployed people In a series of 500 consecutive cases of portal cirrhosis at Charity Hospital in New Orleans, 82 per cent were laborers or unemployed, 71 per cent were men, and 43 per cent were Negroes. The general population of Negroes in this hospital is about 75 per cent, and in Louisiana about 47 per cent

Several etiological factors have been proposed to produce portal cirrhosis. Alcoholism has been considered to be associated with portal cirrhosis for several centuries. Erasistratus of Alexander in 300 B.C. recognized "the stony hard liver with dropsy." Vesalius described "atrophy of the liver" in alcoholics in the Sixteenth Century, and Fernel wrote of wine producing "scirrhus of the liver." Harvey in 1616, James Hart in 1633, Matthew Baillie in 1793, James Johnson in 1820 and Richard Bright in 1827 were among the early investigators to consider that cirrhosis was associated with alcoholic dissipation.[4,70,98] Payne in 1889 published an article, "Discussion of The Morbid Anatomy and Pathology of Chronic Alcoholism," reviewing the historical aspects of alcoholism and portal cirrhosis.[93]

In the current series of 60 necropsy cases of portal cirrhosis, alcoholism was discovered in 76.8 per cent. These patients, incidentally, were evenly divided between hospitals having exclusively private patients and charity patients. In the latter instance, all but 1 of 20 patients were alcoholics. Alcoholism has been defined by Ratnoff and Patek to mean the daily consumption of at least 1 quart of wine, 6 glasses of beer, or 6 ounces of whiskey. They estimated in 1942 that 54 per cent (207 patients) of 386 necropsy cases of portal cirrhosis in New York City were alcoholics.[98] Evans and Gray in 1938 in Los Angeles found 46 per cent of patients with portal cirrhosis were alcoholics, Boles in 1936 in Philadelphia found the incidence to be 30 per cent, Kirshbaum and Shure in 1943 in Chicago, 41.9 per cent, Douglas and Snell in 1950 in Rochester, Minnesota, 64 per cent, and Armas-Cruz and associates in 1951 in Chile, 78 per cent.[1,14,33,38,65] In Syria, Turkey, Iraq, and South India where cirrhosis is common, alcoholism is considered low. Ratnoff and Patek have stated the incidence of cirrhosis among chronic alcoholics varies from 1 to 30 per cent. They found the duration of alcoholism preceding the onset of hepatic failure averaged fifteen years. It has been found that the mortality rate of cirrhosis declined markedly during periods of prohibition in the United States, and in England during World War I and the past several years.[98,107,117] The increased incidence after repeal of prohibition has been recognized

by Spellberg in the Cook County Hospital in Chicago (1.74 per cent in 1932 and 4.15 per cent in 1937) and confirmed by others (Table I).[14,30,117]

TABLE I

ETIOLOGIC FACTORS OF PORTAL CIRRHOSIS

(60 cases)

Malnutrition (alcohol)	46 cases	(76.8%)
Hepatitis	4 cases	(6.7%)
Cryptogenic	10 cases	(16.5%)

It then appears that alcoholism is a definite precursor, although not the most important pathogenetic factor of portal cirrhosis. Alcoholics are notoriously poor eaters, and, despite seemingly good nutrition, their daily ingestion of protein is abnormally low.[illegible] The alcoholic has a poor appetite, has numerous gastrointestinal complaints, is habituated or addicted to drugs, has a distaste for protein and intolerance to fat, and probably has little interest in his diet. He will not spend money for proper nutrition. With few exceptions, the nutritional habits of alcoholics and patients with alcoholic portal cirrhosis are poor.[illegible] Avitaminosis, muscular wasting, and negative nitrogen balance, starvation ketosis, and feminization are commonly observed in these conditions. Douglas and Snell, and Armas-Cruz and his associates, have found normal dietary habits in a significantly high number of cirrhotics.[3,33]

The importance of nutritional deficiency in the production of portal cirrhosis has been emphasized by investigators throughout the world. Tyagaraja in Ceylon, Davies in South Africa, Trowell in East Africa, Waterlow in British West Indies, Armas-Cruz and associates in Chile, Himsworth and Sherlock in England are among those throughout the world who have demonstrated that diets deficient in protein are the important condition associated with or producing portal cirrhosis.[illegible] In this country, Ratnoff and Patek found 17 per cent, Patek and his associates, 73 per cent, and Olsen, 25 per cent of patients with portal cirrhosis and malnutrition.[illegible] Connor has traced the sequential development of cirrhosis in chronic alcoholics with fatty infiltration of the liver.[23,24] Malnutrition occurs in such

diseases as chronic ulcerative colitis, regional enteritis, fibrocystic disease of the pancreas, chronic relapsing pancreatitis, tuberculosis, and sprue Fatty livers are frequently seen in these conditions to progress to portal cirrhosis Malnutrition with diabetes mellitus or alcoholism together have been considered pathogenetic factors of portal cirrhosis by some investigators [20-24, 47, 57, 88, 99, 117, 120] Fatty livers depleted of glycogen due to prolonged malnutrition, particularly protein deficiency, are less resistant to the hepatotoxic effect of alcohol or acute hepatitis. The alcoholic with a fatty liver or fatty cirrhosis contracts infectious hepatitis, on the other hand, which may be eventually fatal, death being due to *bronchopneumonia or hepatic insufficiency. Upon pathological* examination, this liver appears as a chronic toxic hepatitis or "florid cirrhosis" Chvostek and Eppinger independently considered that there may be a constitutional predisposition to the development of portal cirrhosis, and others have assumed the *presence of a biogenetical trait or biochemical variability.*[28]

In the current series of 60 necropsy cases of portal cirrhosis, 6 7 per cent of the cases had a history of antecedent jaundice. A history of jaundice was present in other series of cases of portal cirrhosis as follows. 17 per cent of 100 patients and 3 per cent of 100 controls in the series of Howard and Watson; 25.7 per cent of 208 patients and 18.3 per cent of controls by Armas-Cruz and associates, 6 5 per cent of 386 patients by Ratnoff and Patek; 14 per cent of 269 males and 12 per cent of 107 female patients by Eppinger; in Southern India, 8 of 64 patients by Rao; 4 of 41 patients by Bloomfield, 36 of 71 patients by Fagin and Thompson, 13 of 43 patients by Baggenstoss and Stauffer; and 3 of 100 patients by Koszalka and associates.[1,5,12,30a,40,55a,67,98,117] That portal cirrhosis is a sequelae of viral hepatitis has been the contention of most investigators and denied by a smaller group.[2, 9, 12, 31, 58-61, 63, 65, 66, 68, 69, 75, 103, 105, 107, 112, 115, 117, 125] There appears little doubt that viral hepatitis may progress to a cirrhosis, which may be portal or postnecrotic, or even primary biliary or cholangiolitic in type as determined by serial hepatic biopsies However, a typical history of viral hepatitis, so necessary in order to label cirrhosis as posthepatitic, is often difficult to elicit from a patient with cir-

rhosis. As Perkins has stated, "without more definite knowledge concerning the pathogenetic factors in cirrhosis, it is not possible to answer the question whether previous jaundice in cirrhosis represents previous viral hepatitis, or whether it represents a usual manifestation in the natural development and course of cirrhosis." [94]

PATHOLOGICAL FEATURES

The liver of portal cirrhosis may vary in size, but the pathognomonic feature is the uniformly, granular, regenerative nodules.[105] The diameter of these nodules varies from 1 to 5 mm. in contrast to larger ones present in postnecrotic cirrhosis (Fig. 1). Table II demonstrates the important pathological findings in two groups of necropsy cases of portal cirrhosis. The small livers have been termed "atrophic cirrhosis," and the larger ones "hypertrophic cirrhosis." These descriptive terms are confusing and have mere pathological connotation. The size of the liver of portal cirrhosis varies in the reported series. Invariably, the longer a patient lives with active portal cirrhosis the smaller his liver becomes. Enlarged cirrhotic livers tend to be soft, fatty, and vascular



FIG. 1a. Posthepatitic portal cirrhosis. Weight of liver was 910 gm. Patient died of hepatic insufficiency. Note granular regenerative nodules.

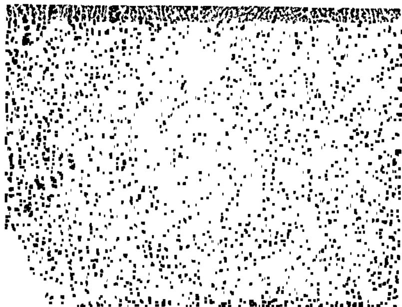


Fig 1b Needle biopsy of liver of same case hepatocellular necrosis, fibrosis and nodular regeneration, infiltration of hepatic parenchyma and stroma with round cells, reduplication of bile ducts H & E (X50)

whereas the smaller cirrhotic livers are hard, fibrotic and less fatty. The color of the liver tends to be yellow when fatty red when congested and green when icteric (Fig 2) (Table II)

Enlargement of the spleen occurs in 25 to 50 per cent of cases of portal cirrhosis The average weight of the spleens in portal cirrhosis is usually between 400 and 500 gm. Ratnoff and Patek's average weight of 111 spleens was 420 gm (30 to 1,700 gm.).[98] Hall, Olsen, and Davis found enlarged spleens in about 65 per cent of 782 cases as did Kirshbaum and Shure in 329 of 351 spleens in cases of portal cirrhosis [48,63]

Esophageal varices were present in 28 6 per cent of cases of portal cirrhosis from the Cook County Hospital necropsy series reported by Spellberg, in 50 per cent of cases of Hall, Olsen and Davis, and in 48 per cent of Patek's series [48 92 93 117] The incidence of 27 of 38 cases of bleeding esophageal varices of the present series appears unusually high Routine esophagoscopy or even





Fig. 1c (*Upper*) Fatty liver in a forty-one year-old female alcoholic patient smooth glistening yellow surface Death due to hepatic insufficiency from eroded esophageal varices (no cirrhosis present) Weight of liver 3450 gm Patient had bilateral hydrothorax and ascites Direct and total serum bilirubin 22.8 and 37.8 mg/100 cc cephalin-cholesterol flocculation 2+ in 48 hrs thymol turbidity 3.6 zinc sulfate turbidity 5.8, serum albumin and globulin 2.1 and 2.8 gm/100 cc blood ammonia 15 ug/100 cc, prothrombin time (Quick) 34 per cent of normal

Fig. 1d (*Lower*) Sagittal section of same liver and spleen Weight of spleen 150 gm

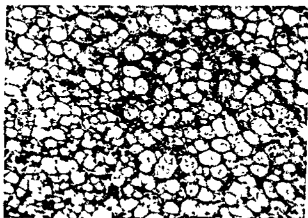


FIG. 1e Section of liver (Fig 1c, 1d). Extensive fatty infiltration No cirrhosis (H & E, X50).

esophagogastroscopy in cases of cirrhosis increased the incidence of esophageal and gastric varices observed in this condition. Hemorrhage from esophageal varices is more commonly due to peptic erosion than to rupture Massive gastrointestinal hemorrhage in cases of portal cirrhosis may originate from sources other than esophageal varices, e g, gastric varices, hemorrhagic gastritis, diffuse hemorrhagic gastroenteritis and duodenal or gastric ulcers Järvinen and Leikola have reported three cases of portal cirrhosis in which death was due to diffuse gastrointestinal hemorrhage in the absence of esophageal varices.[36] The association of hemorrhagic peptic ulcers has been supported by several investigators [73,87,98]

The incidence of primary hepatocellular carcinoma or hepatoma in portal cirrhosis may vary from 4 3 to 11.6 per cent (Fig. 3) [10,37,78,132] That most cases of hepatoma are associated with cirrhosis has been demonstrated by Greene who found cirrhosis occurring in 61.3 per cent of 1,073 cases of hepatoma.[46] Hayne and Kernohan found that 75 per cent of cases of hepatoma and only 18 2 per cent of cholangiomas had coexisting cirrhosis[51] McNamara and his associates found cirrhosis in 92 per cent of hepatomas and in 28 per cent of cholangiomas.[79] MacDonald reviewed autopsied cases at the Boston City Hospital from 1917 to 1954 and noted

an increase in primary carcinomas of the liver with cirrhosis[24] He ascribed this to be the result of more cases of "healed acute yellow atrophy" and fatty nutritional cirrhosis, increased longevity of patients, and possible increased alcoholic inhibition, malnu-

TABLE II
PERTINENT NECROPSY DATA OF 60 CASES OF PORTAL CIRRHOSIS

		Baggenstoss & Stauffer (43 cases)
Weight of Liver		
Largest, gm	4,050	4,500
Smallest, gm	883	675
Mean weight gm	2,250	2,474
Weight of spleen		
Largest, gm	940	
Smallest, gm	110	
Mean weight, gm.	344	456
Esophageal varices	39	32
Ruptured	27	11
Hemorrhagic gastritis	13	—
Ascites	46	39
Hydrothorax	24	14
Bronchopneumonia	27	—
Hepatoma	3	3
Cholangioma	1	0



FIG 2 Fatty alcoholic portal cirrhosis, sagittal section liver colored glistening yellow Note granular regenerative nodules Weight 2,150 gm Death due to esophageal hemorrhage from eroded varix

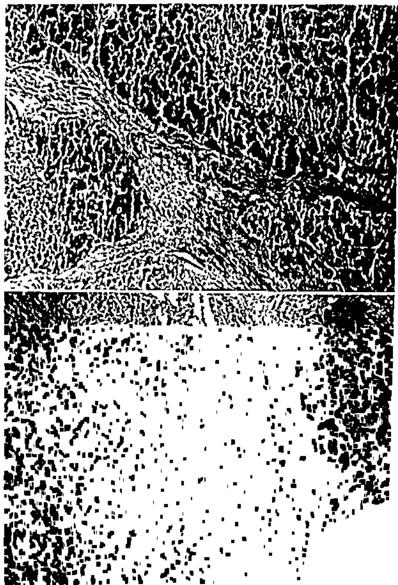


Fig 3a (*Upper*) Needle biopsy of liver. Hepatoma and portal cirrhosis (H & E, X50)

Fig 3b (*Lower*) Needle biopsy of liver Cholangioma and portal cirrhosis (H & E, X50).

trition and viral hepatitis. The incidence of cirrhosis and hepatoma reported among South Africans by Gillman and Gillman is the highest in the world.[44] Cirrhosis was found to occur in one-third of a series of cases of sarcoma of the liver.[53,114] Foote has also recorded hemangio-endotheliosarcoma complicating cirrhosis in children.[45] I have performed needle biopsies of the liver in 16 cases of hepatoma of which 10 cases were portal cirrhosis (Fig. 3a), 3 cases hemochromatosis, and 2 definite cases of postnecrotic cirrhosis. Portal cirrhosis and cholangioma recently were found in the same patient by needle biopsy [illegible] have demonst[illegible] in cirrho[illegible]

The [illegible]ogical features of portal cirrhosis have been alluded to previously (Chapter 3). Baggenstoss and Stauffer studied portal cirrhosis, and others too have shown the following histological criteria characteristic of portal cirrhosis.[56,67,70,77,83,85,110,111] The structural pattern of the liver is altered uniformly and the hepatic veins are eccentrically located in the regenerative nodules. These nodules are uniform in size, less than 0.5 cm., and closely set. The regenerative nodules have rare bizarre appearing hepatic cells, and invariably have different amounts of fatty infiltration. There are alcoholic-hyaline bodies present, also, mild to moderate focal necrosis and parenchymal polymorphonuclear leucocytic infiltration (Figs. 1-7). The internodular stroma is narrow, containing collagenous connective tissue and the bile ducts are found to proliferate. In contrast to postnecrotic cirrhosis, the smaller hepatic venules are severely compressed and their inflammatory reaction is rare. A phosphotungstic acid hematoxylin stain may be employed to demonstrate "alcoholic-hyaline bodies," a hyaline cytoplasmic composition in the hepatic cells of portal cirrhosis or fatty livers of chronic alcoholic patients.[illegible]

CLINICAL FEATURES

The initial symptoms and physical findings of portal cirrhosis ensue in an insidious manner and are presumptively diagnostic. These patients may complain of weakness, anorexia, fatigue and indigestion (Table III). These prodromal symptoms often per-



FIG 4 Serial needle biopsies representing the transgression of a fatty liver to a fatty cirrhosis in a forty eight-year old alcoholic male Conventional treatment was not followed

FIG 4a. (*Upper*) Fatty infiltration hepatocellular necrosis and proliferation of stroma (H & E, X50)



FIG. 4c. (*Upper*) At twenty-three months: beginning nodular regeneration, fatty infiltration, fibrosis with reduplication of bile ducts, and marked hepatocellular necrosis (H & E, ×50).

FIG. 4d. (*Lower*) At thirty-two months: active fatty cirrhosis (H & E, ×50), nodular regeneration, fibrosis and marked hepatocellular necrosis.

TABLE III
INCIDENCE OF INITIAL CLINICAL MANIFESTATION IN PORTAL CIRRHOSIS
(53 males, 7 females, youngest age 37, oldest age 75; mean age 56)
(60 cases)

Initial manifestation	*(60 cases)* (%)	*Ratnoff & Patek (107 cases)* (%)
Ascites	27	27 7
Edema	20	9 6
Abdominal pain	20	12 4
Gastrointestinal hemorrhage	10	8 8
Jaundice	8	10 1
Dyspnea	8	(6) *
Exhaustion	6	5 7
Peripheral neuritis	5	—
Pruritus	3	(3) *
Hemorrhoids	3	(2) *
Anorexia	3	2 3
Indigestion	3	4 4
Diarrhea	3	3 6
Nausea and vomiting	2	7.5

* ( ) = cases

sist for years before the typical clinical picture of portal cirrhosis develops. In some instances, the disease remains latent indefinitely, and in others more typical findings such as ascites, edema, gastrointestinal hemorrhage, jaundice, abdominal pain and bleeding tendencies are initial complaints. Presumably, this depends upon the amount of hepatocellular damage, the activity of cirrhosis, the persistence of the pathogenetic factors and an intercurrent disease. Anorexia and loss of weight are often masked by the chronic alcoholic who appears overly obese and seemingly well developed despite malnutrition Though more infrequent than in postnecrotic cirrhosis or hemochromatosis, abdominal pain may be the initial complaint in patients with portal cirrhosis. The character of this pain varies from vague indigestion or postprandial epigastric fullness to steady or colicky epigastric pain Not infrequently, a patient with portal cirrhosis has bouts of colicky epigastric pain associated with tenderness and rigidity over the affected area In this situation, a cholecystogram reveals a nonfunctioning gallbladder and an unnecessary cholecystectomy can be avoided.[27] A tender cirrhotic liver may be due to parenchymal congestion, necrosis, distention or inflammation of Glisson's capsule.[71] Unremitting, progressive hepatic pain occurring in a



FIG 5a (*Upper*) Needle biopsy of liver Portal cirrhosis in a female alcoholic age forty five In this instance there was no fatty infiltration, nodular regeneration, fibrosis and hepatocellular damage (H & E ×50)

FIG 5b (*Lower*) Needle biopsy of the liver of an unusual combination of portal cirrhosis and Gaucher's disease note large foam cells This is a rare concurrence of two unrelated diseases, histological details obscured due to damaged slide (H & E, ×50)

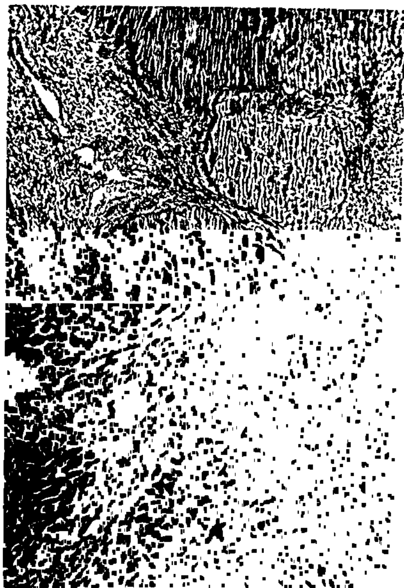


FIG 5c (*Upper*) A necropsy histological section Posthepatitic portal cirrhosis in a fifty three year old woman Infectious hepatitis five years previous with subsequent latent clinical course Small regenerative nodules, fibrosis, hepato-

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patient with cirrhosis should raise the question of a hepatoma. Esophageal hemorrhage or jaundice may be the initial complaint in approximately 10 per cent of patients with portal cirrhosis.

When the eventual symptoms and physical findings of portal cirrhosis occur, the disease should be considered to be advanced (Tables IV and V). Usually these symptoms are not diagnostic and are, generally: anorexia, indigestion, nausea, vomiting, loss of weight, constipation, diarrhea, abdominal pain, abdominal distention, flatulence, distaste for protein, and intolerance to fat,

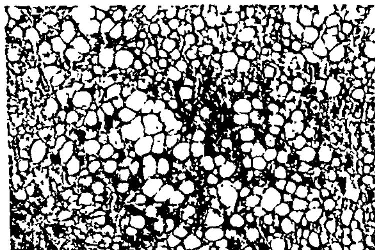


FIG. 6a. Needle biopsy of liver, alcoholic male age fifty-seven: extensively generalized parenchymal fatty infiltration and hepatocellular necrosis. (H & E X50)

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cellular necrosis, and marked round cell infiltration of parenchyma and stroma. (H & E, X30)

FIG. 5d. (*Lower*) Needle biopsy of liver, forty-two year old female: jaundice, ascites, esophageal varices, and marked malnutrition. Similar histological features are observed in addition to extensive hepatocellular necrosis and stasis of bile, not unlike that observed in chronic obstructive jaundice. It was con

malnourished patients with clinicopathological features of obstructive jaundice. (H & E X30)

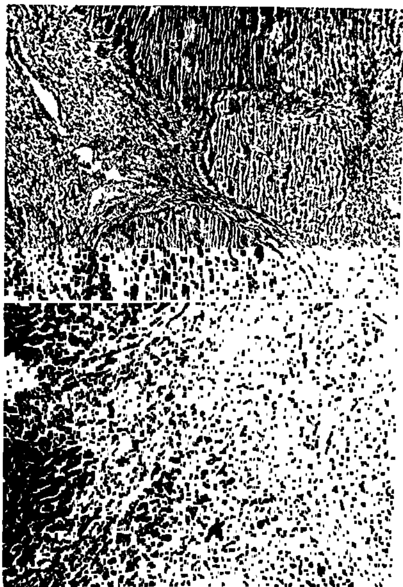


FIG. 5c. (*Upper*) A necropsy histological section Posthepatitic portal cirrhosis in a fifty-three year old woman Infectious hepatitis five years previous with subsequent latent clinical course Small regenerative nodules, fibrosis, hepato-

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roughage, or condiments. Pruritus, one of the most common complaints of cholestatic hepatic diseases, occurs infrequently in portal cirrhosis. Hematemesis has been found in 10 to 30 per cent of cases of portal cirrhosis. In contradistinction to other lesions responsible for gastrointestinal hemorrhage, esophageal variceal

TABLE IX
INCIDENCE OF EXTENSUAL SYMPTOMS IN PORTAL CIRRHOSIS

	Ratnoff & Patek (60 cases)	Ratnoff & Patek (386 cases)	Armas Cruz (209 cases)	Douglas & Snell (444 cases)
Symptoms	(%)	(%)	(%)	(%)
Weakness	95	21.2	—	20.7
Abdominal pain	56	47.7	61	23.4
Weight loss	33	33.4	81	22.3
Dyspnea	35	21.2	—	—
Hematemesis	30	27.4	—	16.2
Nausea	28	33.4	—	—
Vomiting	26	29.8	72	4.2
Diarrhea	20	20.2	30.2	—
Constipation	18	8.5	—	—
Bleeding tendency	16	23.6	—	—
Pruritus	15	3.3	21.6	10.8
Menstrual abnormality	6	3.1	—	—
Melena	28	2.6	15.3	16.4
Anorexia	—	3.5	86.5	8.5
Epistaxis	18	18	—	—

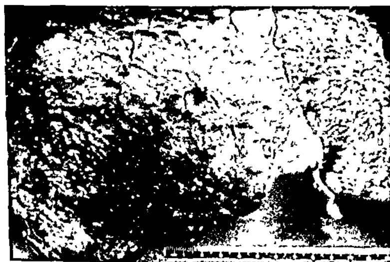


FIG. 6d. Gross liver portal cirrhosis-weight 2,250 gm. (Kleckner, M. S., Jr.—South. M. J.—Jan. 1957.)

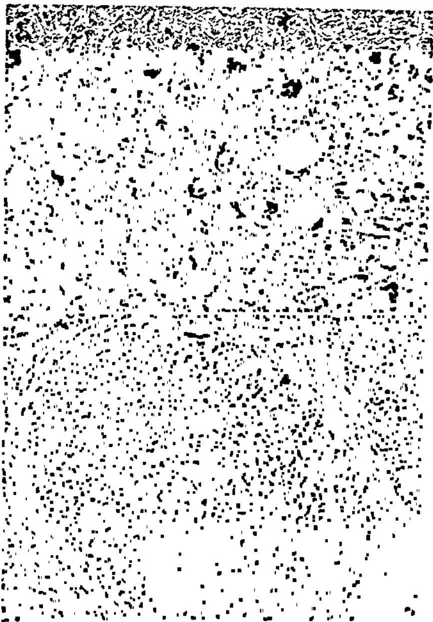


Fig 6b *(Upper)* Same specimen showing hyaline perinuclear cytoplasmic bodies in hepatic cells phosphotungstic acid hemotoxylin stain (X400).
Fig 6c *(Lower)* Same specimen, three one half years later, necropsy section patient died from hepatic insufficiency and hemorrhagic esophageal varices Fatty infiltration is practically absent Portal cirrhosis, hepatocellular necrosis, nodular regeneration and thin fibrous stroma (H & E, X80). (Kleckner, M S, Jr—South M J—Jan, 1957)

TABLE X

INCIDENCE OF PHYSICAL FINDINGS IN PORTAL CIRRHOSIS

Physical signs	(60 cases)	*Ratnoff & Patek* (386 cases)	*Fleming & Snell* (200 cases)†	*Armas Cruz et al* (209 cases)	*Douglass & Snell* (111 cases)
	(%)	(%)	(%)	(%)	(%)
Enlarged liver	90	77.4	55	75.1	70.9
Edema	72	61.1	58	40.8	29.9
Spider angioma	67	15	26	—	26.1
Esophageal varices	60	—	—	—	—
*Enlarged spleen	60	44	31	30.7	32.2
Palmar erythema	60	4	—	45.1	—
Ascites	57	78	100	71	47.7
Loss of hair	57	6.5	—	—	—
Hemorrhoids	34	27.2	—	9.1	—
Abdominal striae	30	—	—	—	—
Jaundice	28	63.9	45	69.5	33.8
Testicular atrophy	22	—	—	—	—
Fever	18	21.5	—	30.7	—
Gynecomastia	17	—	—	7.64	—
Umbilical hernia	14	11.1‡	—	—	—
Ecchymosis	6	—	—	—	—
Clubbed fingers	6	5.4	—	—	—
Caput Medusae	5	1	—	—	—
Hydrothorax	5	6.5	—	8.6	—
Visible collateral circulation	—	23.6	11	63	18.5
*Hypersplenism	10				

†Entire series with ascites

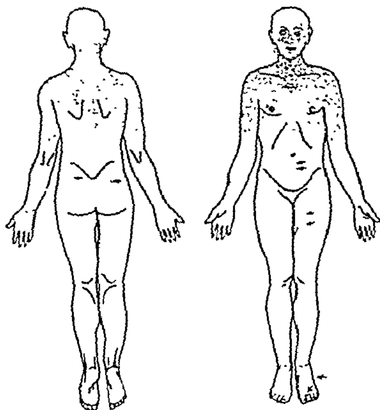
‡All hernias



FIG 7 Needle biopsy of the liver Posthepatitic portal cirrhosis Infectious hepatitis occurred five years before the onset of weakness, edema, ascites and loss of weight During the interim the course was latent (H & E X80)

hemorrhage tends to be massive, bright red, managed with difficulty, and may be controlled with tamponade using an esophagogastric balloon Gastrointestinal hemorrhage in portal cirrhosis may also be caused by thrombocytopenia as the result of hypersplenism, duodenal and gastric ulcers, acute hemorrhagic gastritis, esophagogastric lacerations (Mallory-Weiss syndrome), neoplasms, increased capillary fragility, and hypoprothrombinemia (Chapter 14). In the later instance, hemorrhage may ensue from the nose, mouth, kidneys, bladder, urethra, rectum, and vagina

The pertinent physical findings in several groups of portal cirrhosis are listed in Table V They are more important diagnostically than symptoms and possibly laboratory information These are hepatosplenomegaly, ascites, edema, palmar erythema, loss of body hair and spider angioma, often occurring in combination (Fig 8). The student learns that statistics of the physical findings of portal cirrhosis can be unreliable, and it is best to evaluate the cirrhotic patient individually Whereas one



PERSONS WITH HEPATIC DISEASES

DISTRIBUTION OF "SPIDERS"

Fig. 16. Distribution of spider angioma in hepatic disease (Courtesy Bean W B—Medicine—1945)

bronchopneumonia An unremitting fever on the other hand usually heralds an unfavorable diagnosis and indicates progressive hepatocellular necrosis Evidence of gonadal dysfunction such as, sterility, amenorrhea, oligomenorrhea and menorrhagia and feminization in the male, gynecomastia testicular atrophy, loss of libido, impotency, soft skin, and alopecia, especially in the

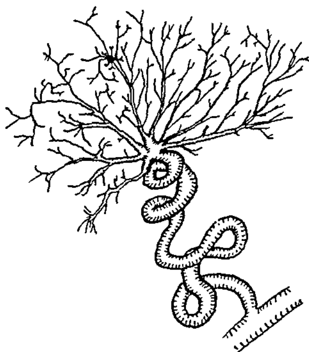


FIG 8a Spider angioma Coiled cutaneous arteriole (Courtesy, Bean, W B — Medicine—1945)

cirrhotic may demonstrate physical stigmata another may have only a mildly enlarged spleen despite liver biopsies which are indistinguishable Usually the patient with portal cirrhosis and alcoholism may be the roly-poly, happy-go-lucky, careless character of the ward, or, on the other hand, have predominant neuropsychiatric features such as hemorrhagic polioencephalitis (Wernicke's disease), Korsakoff's syndrome, delirium tremens, agitated depression, impending hepatic exogenous (ammoniagenic) coma, polyneuritis, "chronic brain disease" or drug intoxication The patient with portal cirrhosis frequently has a low-grade fever associated with leukocytosis and possibly subclinical jaundice especially following an alcoholic debauch. Also these patients commonly are susceptible to intercurrent infections, particularly



Fig 8d Clubbed fingers and white fingernails in a patient with portal cirrhosis

ment. The presence of spider angioma should arouse the suspicion of cirrhosis with esophageal varices and is a more reliable physical finding of this condition than palmar erythema Parotid swelling has been noted in alcoholic patients with cirrhosis and malnutrition [15,35,106,108,118,134] Wolfe and his associates have noted the association of Dupuytren's palmar contracture with alcoholism and portal cirrhosis [133] Jaundice occurring in patients with cirrhosis may be terminal or associated with superimposed viral hepatitis, intercurrent infection, recent alcoholic dissipation, hepatic neoplasm or icterogenic medications Progressive jaundice in portal cirrhosis, however, is an ominous sign of severe hepatic insufficiency whether due to the natural disease or hepatoma Umbilical, ventral, inguinal, diaphragmatic and epigastric hernias are commonly seen in cirrhosis, particularly when ascites has been present (Fig 10). Umbilical and diaphragmatic hernias are more commonly observed as the result of increased intra-abdominal pressure due to ascites Clubbed fingers and curved

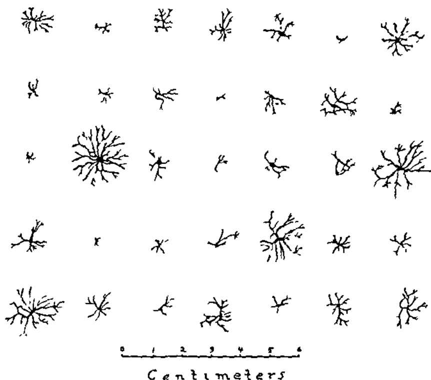


FIG 8c Various types of cutaneous spider angioma (Courtesy, Bean, W B — Medicine—1945)

pectoral and axillary areas, are common findings[8,17,19] Bennett and his associates found the pathological incidence of testicular atrophy and gynecomastia markedly increased and a benign enlarged prostate gland low in patients with cirrhosis.[7]

Spider angioma, in the area of the venous distribution of the superior vena cava, and palmar erythema are found not only in patients with cirrhosis but in such conditions as pregnancy, avitaminosis B_1, thyrotoxicosis, rheumatic fever, rheumatoid arthritis, xeroderma pigmentosum, chronic irradiation dermatitis, lupus erythematosus, Raynaud's disease and Cushing's disease.[6,89] (Fig. 9). These two valuable diagnostic signs of cirrhosis often become more intense and increase in size and number when the disease progresses, and may even subside with clinical improve-

finger nails are infrequently seen in advanced portal cirrhosis, probably as a manifestation of malnutrition. The nail beds in patients with cirrhosis may disclose such characteristic changes as white nails, red half-moons, and opaque onychodermal bands as physical signs of this condition.[81,121] The incidence of arterial hypertension is lower in cases of portal cirrhosis as compared with non-cirrhotics.[45,118] Loske studied 504 cases of cirrhosis and found that arterial hypertension was uncommon, that arterial hypertension was reversible after the clinical onset of cirrhosis, and that



FIG. 9c. Marked ascites, umbilical hernia, hepatosplenomegaly, gynecomastia (?), pectoral alopecia, abdominal venous collateral circulation in a fifty-three year old male alcoholic with portal cirrhosis, minimal to moderate hepatic insufficiency and minimal hypersplenism, necessitating multiple abdominal paracenteses. This case also illustrates the unbelievable clinical benefit after one and one half to two years of conventional ambulatory therapeutic management of this condition. At the end of this period of time there was no endoscopic evidence of pre-existing esophageal varices, clinical jaundice, ascites and edema. Spider angioma and palmar erythema were inconclusive. The hepatic function tests became nearly normal and the bromsulfalein dye excretion test was 12 per cent at 45 minutes.



Fig 9a Torso of an alcoholic patient with hepatosplenomegaly, ascites, umbilical hernia, abdominal venous collateral circulation, pectoral alopecia and gynecomastia—feminizing physical features

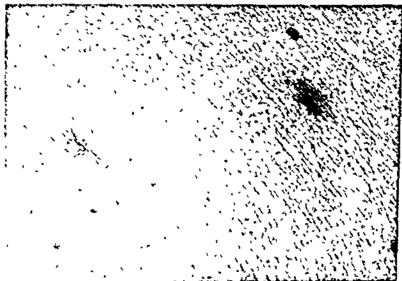


Fig 9b Several spider angioma, the larger one pulsating, over the region above the superior vena cava

TABLE VI

LABORATORY DATA IN PORTAL CIRRHOSIS

Laboratory Data	(60 cases) (%)	*Hall, Olsen, & Davis (782 cases)*
Leukopenia	15	
Leukocytosis	31	66
Thrombocytopenia	28	—‡
Normochromic, normocytic anemia	16	
Hypochromic microcytic anemia	7	290
Hyperchromic macrocytic anemia	6	
Hemolytic anemia	2	—
Hypoalbuminemia	51	320
Hyperglobulinemia	46	239
Abnormal cephalin-cholesterol flocculation	41	—
Abnormal thymol turbidity	49	—
Abnormal zinc sulfate turbidity	22 (24 cases)†	—
Elevated plasma alkaline phosphatase	19	—
Elevation of serum iron	4 (9 cases)	—
Low serum cholinesterase	4 (9 cases)	—
Hypoprothrombinemia	17	200
False positive blood serology	5	74*
Low cholesterol-cholesterol esters	14 (34 cases)	31/41
Average BSP determination 45	23	—
Average sedimentation rate (Westergren)	45	—
Average direct and indirect serum bilirubin	1.7	236
	2.8	—

*Positive

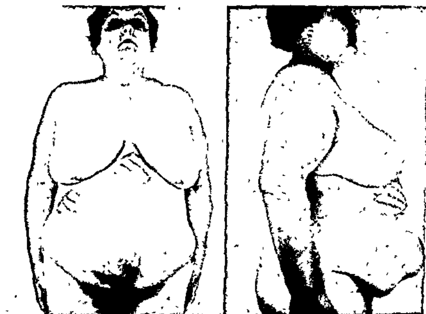
†( ) cases rather than percent

‡—"icterus index"

and zinc sulfate turbidity tests, hypoalbuminemia and hyperglobulinemia[14 25-7 32 34 37 40 47 45 61 66 81 95-97 101 131]. Hypergammaglobulinemia, decreased blood cholesterol esters, hypoprothrombinemia, thrombocytopenia, hyperbilirubinemia suggest advanced cirrhosis in which the prognosis is poor. Plasma electrophoretic determinations usually reflect depressed albumin and elevated gamma globulin levels and are presumptively diagnostic. The use of the determination of serum iron, cholinesterase, transaminase, and mucoprotein of the serum in portal cirrhosis are discussed in Chapter 16[41 61 127]. While some of the newer hepatic function tests afford no diagnostic information in a case of portal cirrhosis, serial determinations of serum transaminase and cholinesterase, in particular, are extremely sensitive and are reflective of hepatocellular dysfunction.

an inverse relationship existed between the serum albumin-globulin ratio and arterial hypertension.[74] Dyspnea, orthopnea, cyanosis, and cough are some common respiratory findings in patients with cirrhosis particularly with ascites, which reduces the vital capacity of the lungs

Zieve has called attention to an unusual syndrome associated with alcoholic fatty liver or cirrhosis consisting of jaundice, hyperlipemia and hemolytic anemia[137] The latter features recede upon cessation of alcoholic imbibition



Figs 10a and b A patient with cryptogenic portal cirrhosis as well as portal cirrhosis obesity, ascites, umbilical hernia, caput medusae, palpably enlarged liver, furunculosis, and tinea conditions

LABORATORY FINDINGS

The laboratory data of 60 cases of advanced portal cirrhosis are listed in Table VI. The biochemical tests most commonly indicative of cirrhosis are the bromsulfalein dye excretion test, hepatic flocculation tests, including the more commonly employed *such as the* cephalin-cholesterol flocculation and thymol

in 1912 by Armstrong and his associates who were aware of its obscure definition.[3] They reviewed thoroughly 52 previously published reports and 3 of their own cases of Cruveilhier-Baumgarten disease and recommended that the term Cruveilhier-Baumgarten syndrome be applied clinically to any patient with portal hypertension, generally with splenomegaly, and in whom evidence exists of excessively prominent umbilical circulation in the form of visible superficial veins, loud abdominal murmur and thrill. They considered Cruveilhier-Baumgarten disease, on the other hand, to be any case with necropsy evidence of patency of the umbilical vein or congenital hypoplasia of the portal system itself together with atrophy and little or no fibrosis of the liver. This disease may be a manifestation of extrahepatic portal hypertension.[50,122,124] However, because cirrhosis may occur in this condition and produce intrahepatic portal hypertension, it is necessary to perform a careful needle biopsy of the liver for confirmation. The disease may be associated with portal or postnecrotic cirrhosis. The salient physical findings, largely dependent upon portal hypertension, consist of an abdominal venous murmur and thrill loudest in the umbilical and epigastric regions, dilated thoraco-abdominal veins and splenomegaly. Hypersplenism may occur in this condition. Cirrhosis together with patency of the umbilical vein may be responsible for portal hypertension, as observed in one necropsy case, and has been found in more than 90 per cent of cases of Cruveilhier-Baumgarten disease according to Cheng.[22] Wollaeger and Shands report the concurrence of Cruveilhier-Baumgarten syndrome with hepatolenticular degeneration.[125]

Venograms may demonstrate in the living patient a patent umbilical vein communicating with the portal venous system with radiopaque dye and has been utilized by Celis and his associates.[18] Another method of illustrating abnormal systemic venous communication with the portal vein consists of demonstrating higher levels of blood glucose in the veins of the abdominal wall in contrast with blood obtained from the antecubital area one hour after oral ingestion of dextrose.[22,113] Treatment of the Cruveilhier-Baumgarten syndrome is medical. Kennedy and Rousse-

LATENT CIRRHOSIS

Cirrhosis asymptomatic following treatment, coincidentally diagnosed pathologically during an abdominal surgical exploration or observed at necropsy, has been termed latent cirrhosis. Approximately 50 per cent of Ratnoff's necropsy cases of portal cirrhosis were[96,97,101] considered clinically latent.[78,98,102] For the most part, it is assumed that they offer neither definite nor objective evidence of hepatic insufficiency, ascites and portal hypertension. This condition, however, may relapse due to any affection that augments hepatocellular necrosis. The susceptibility of the hepatic cells in the regenerative nodule to anoxia, intercurrent disease, hepatotoxic drugs, or physical stress is generally appreciated. Recently, five latent cases of cryptogenic portal cirrhosis became symptomatic in the course of bronchopneumonia, alcoholic debauch, acute hemorrhagic duodenal ulcer, acute *brucellosis*, and inguinal herniorrhaphy, respectively. *Patients with* portal cirrhosis who recover from hepatocellular damage and lead a salubrious life may anticipate normal life expectancy.

CRUVEILHIER-BAUMGARTEN SYNDROME

In 1833, Fagot described an alcoholic soldier in whom a loud venous umbilical bruit, caput medusae, and dilated abdominal veins were present.[3] Necropsy revealed a small, noncirrhotic liver, enlarged spleen and a wide patent umbilical vein. Cruveilhier in 1835 elaborated on the details of this case and believed that hepatic atrophy was due to a congenitally defective umbilical circulation.[26] Bamberger in 1851 and Trousseau and Sappey in 1868 described, respectively, the necropsy findings of a case of cirrhosis *with patent periumbilical vein in which an abdominal* venous hum and thrill were audible.[3] In 1907 Baumgarten reported a case of a sixteen-year-old boy who had weakness, ascites, dilated abdominal veins, enlarged spleen, anemia, and leukopenia, who died of a gastric hemorrhage.[126a] Necropsy revealed patency of the umbilical vein and atrophic liver without cirrhosis, which he thought to be congenital in origin. In 1922, Hanganutz introduced the term "Cruveilhier-Baumgarten cirrhosis." The most authoritative investigation of this syndrome was reported

in 1912 by Armstrong and his associates who were aware of its obscure definition.[4] They reviewed thoroughly 52 previously published reports and 3 of their own cases of Cruveilhier-Baumgarten disease and recommended that the term Cruveilhier-Baumgarten syndrome be applied clinically to any patient with portal hypertension, generally with splenomegaly, and in whom evidence exists of excessively prominent umbilical circulation in the form of visible superficial veins, loud abdominal murmur and thrill. They considered Cruveilhier-Baumgarten disease, on the other hand, to be any case with necropsy evidence of patency of the umbilical vein or congenital hypoplasia of the portal system itself together with atrophy and little or no fibrosis of the liver. This disease may be a manifestation of extrahepatic portal hypertension.[20, 122, 124] However, because cirrhosis may occur in this condition and produce intrahepatic portal hypertension, it is necessary to perform a careful needle biopsy of the liver for confirmation. The disease may be associated with portal or postnecrotic cirrhosis. The salient physical findings, largely dependent upon portal hypertension, consist of an abdominal venous murmur and thrill loudest in the umbilical and epigastric regions, dilated thoraco-abdominal veins and splenomegaly. Hypersplenism may occur in this condition. Cirrhosis together with patency of the umbilical vein may be responsible for portal hypertension, as observed in one necropsy case, and has been found in more than 90 per cent of cases of Cruveilhier-Baumgarten disease according to Cheng.[22] Wollaeger and Shands report the concurrence of Cruveilhier-Baumgarten syndrome with hepatolenticular degeneration.[135]

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lot and Santz reported, however, successful surgical results following splenectomy and a splenorenal shunt.[62, 109]

PRINCIPAL AND CONTRIBUTING CAUSES OF DEATH

The chief causes of death from portal cirrhosis are hepatic insufficiency, esophageal variceal hemorrhage, hepatoma, bacterial infections, thrombosis of the portal vein, hypersplenism, postoperative complications, malnutrition and alcoholism (Table VII).[32, 129] Patek found glomulonephritis in 7 per cent of 200 cases of portal cirrhosis and portal vein thrombosis accounted for 8 of 75 deaths in Patek's series.[56, 90-92] Metastatic carcinoma has been noted rarely in cirrhosis.[72] Tuberculosis nowadays is an unusual cause of death in portal cirrhosis compared to earlier statistics of about 10-15 per cent. Sudden death has been described due to fatty embolism from a fatty liver.[36, 54]

PROGNOSIS

Figures 11, 12 and 13 demonstrate the survival rates of patients with portal cirrhosis as compared with postnecrotic cirrhosis after the initial onset of hematemesis, jaundice, or ascites since the advent of a dietary regimen consisting of a high-caloric, high-protein diet. These curves were obtained from record-room and necropsy data from 1935 to 1949, and *do not* show the remarkable and improved therapeutic advances, particularly in the last decade. In considering survival rates in cirrhosis, one should consider the socio-economic status of the patient or community together with the quality of modern medical and surgical treatment. The mortality of advanced cirrhosis, particularly following gastrointestinal hemorrhage, is high, almost 50 per cent from one to two years from the onset of hemorrhage. Surgical relief of this complication as we shall see affords considerably better prognosis (Chapter 14). Ratnoff and Patek in 1942 found that, following esophageal hemorrhage in cases of portal cirrhosis, 40 per cent died in one month, 70 per cent in one year, and 80 per cent within seven years.[95] They found that following ascites 39 per cent survived at the end of one year, 21 per cent at two years, and 7 per cent at five years. Contrast these statistics with Patek's report in 1948 which shows that following ascites, 65 per cent

TABLE XII
CAUSES OF DEATH IN PORTAL CIRRHOSIS

	(60 cases)	*Ratnoff & Patek* (213 cases)	*Patek* (44 cases*)	*Baggenstoss & Stauffer* (31 cases)
	(%)	(%)		(%)
Immediate cause				
Hepatic insufficiency	(11)	56.2	(7)	58.1
Bleeding esophageal varices	(27)	25.8	(13)	25.8
Hepatoma (intraperitoneal hemorrhage)	(1)	—	—	—
Hemorrhagic gastroenteritis	(6)	—	—	(7)‡
Pneumonia	(6)	10.5	(6)	4.2
Glomerulonephritis	(1)	—	(5)	—
Bleeding duodenal ulcer	(1)	—	—	—
Giant follicular lymphoma	(1)	—	—	—
Congestive heart failure	(2)	(2)†	—	—
Diabetic coma	(1)	—	—	—
Peritonitis	—	4.6	(1)	4.2
Thrombosis of Portal Vein	—	(1)†	(8)	—
Contributory cause of death				
Pneumonia	(9)	—	—	(1)†
Postoperative death	(7)	16	—	—
Thrombosis of portal vein	(6)	(1)	—	—
Hepatoma	(2)	—	—	(3)†
Cholangioma	(1)	—	—	—
Thrombocytopenic purpura	(1)	—	—	—
Tuberculosis	(1)	—	—	—
Cerebral thrombosis or hemorrhage	(1)	(1)†	(3)	—
Perforated duodenal ulcer	(1)	—	—	—
Pulmonary complications		—	—	(5)†

*2 cases of pericarditis and 1 of bacterial endocarditis
†( ) cases rather than per cent
‡( )Hemorrhage from sources other than varices

lot and Santz reported, however, successful surgical results following splenectomy and a splenorenal shunt[62,109]

PRINCIPAL AND CONTRIBUTING CAUSES OF DEATH

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Survival after onset of jaundice in 10 cases of Laennec's (portal) cirrhosis and 18 of postnecrotic cirrhosis

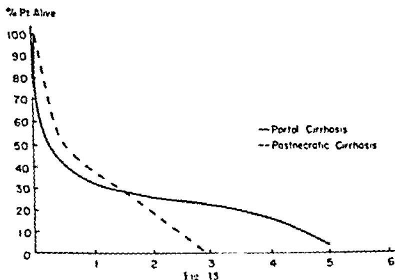


Fig 15

survived at the end of one year, 50 per cent at the end of two years, and 30 per cent at the end of five years.[82] Ratnoff and Patek in 1942 found that approximately 25 per cent of cases of portal cirrhosis survived one year after the onset of jaundice, nearly 20 per cent two years, and 10 per cent five years[84] Douglass and Snell found a mortality of 53 per cent in the first year in cases of portal cirrhosis with clinical jaundice and no survivors in seven years[23] The current prognosis of portal cirrhosis is not so glib as some of the earlier reports appear to indicate As Spellberg emphasized in comparing groups of cirrhotics studied during different periods of time with and without the benefit of intensive medical therapy, the modern management of cirrhosis offers much more hope and better prognosis[illegible] One should therefore, not rely too much on obsolete survival rates since modern therapy affords more encouraging results The prognosis of early cirrhosis is reasonably good and more and more latent cirrhotics are observed in clinical practice

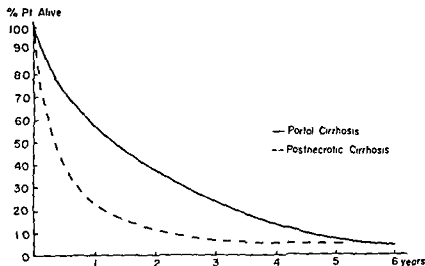

Survival after onset of ascites in 26 patients with Laennec's (portal) cirrhosis and 18 with postnecrotic cirrhosis
% Pt Alive
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6 years
— Portal Cirrhosis
-- Postnecrotic Cirrhosis

FIG 11.

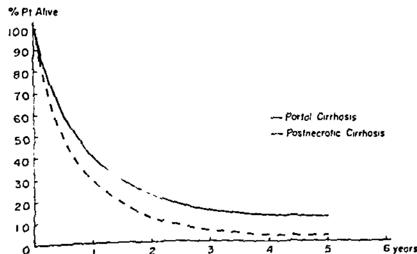

Survival after first hematemesis in 10 cases of Laennec's (portal) cirrhosis and 18 of postnecrotic cirrhosis
% Pt Alive
100
90
80
70
60
50
40
30
20
10
0
1
2
3
4
5
6 years
— Portal Cirrhosis
-- Postnecrotic Cirrhosis

FIG 12

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liary cirrhosis. Consequently, the only unfailing distinction of postnecrotic cirrhosis is the gross morphological appearance. However, if one is able to obtain a specimen by needle biopsy measuring from 2.5 to 4.0 cm in length, it may be possible to arrive at a correct pathological diagnosis. It is not unusual, on the other hand, to have a histological diagnosis of portal cirrhosis obtained by needle biopsy and to arrive at a gross pathological diagnosis of postnecrotic cirrhosis during laparotomy, peritoneoscopy or at necropsy. Consequently, the histological diagnosis of postnecrotic cirrhosis is only presumptive particularly if the irregular regenerative nodules, which are larger than 1 cm. in diameter, are fragmentary in the hepatic specimen

In 1849, Rokitansky referred to pure, red atrophy of the liver, implying the discoloration of many specimens of postnecrotic cirrhosis.[73] Bright in 1828, Marchand in 1895, MacDonald and Milne in 1909, Mallory in 1911 and Pratt and Stengal in 1927 were among the first to describe this specific type of cirrhosis. They used such terms as multiple nodular hyperplasia, toxic cirrhosis, healed yellow atrophy or subacute diffuse necrosis of the liver[56, 57, 70] This condition has also been described as chronic yellow atrophy of the liver, subacute necrosis or atrophy of the liver and subacute and chronic hepatitis[9, 19, 47, 54, 79] In 1932, Judd and Beaver described the clinical and pathological picture of 22 cases of atrophy of the liver, of which 10 cases were toxic or postnecrotic cirrhosis, in which the clinical duration was from thirty-two days to three years[41] Himsworth emphasizes the term postnecrotic scarring rather than postnecrotic cirrhosis[34] Karsner in 1943 first coined the term "postnecrotic cirrhosis" as one of ten types of cirrhosis[43] In order to appreciate the clinical and pathological features of postnecrotic cirrhosis, 60 necropsy cases have been studied in a manner similar to the investigations of Baggenstoss and Stauffer and Ratnoff and Patek[4, 45, 72, 73]

ETIOLOGY

The pathogenetic factors of postnecrotic cirrhosis which are usually recognized are viral hepatitis and hepatotoxic agents. Postnecrotic cirrhosis, on the other hand, may be demonstrated in the various cirrhoses of infants and children, hepatolenticular

Chapter 7

POSTNECROTIC CIRRHOSIS

INTRODUCTION

THIS PARTICULAR type of cirrhosis, which has become more increasingly recognized, has definite morphological implications and is characterized principally by atrophy, large irregularly distorted regenerative nodules, wide zones of internodular stroma, and moderate to severe focal necrosis of the liver. It occurs more frequently in women, is presumed to be a residual of acute fulminant viral or toxic hepatitis, and is, predominantly, less amenable to conventional therapeutic management than is portal cirrhosis. Postnecrotic cirrhosis is generally characterized clinically by hepatic insufficiency which may be progressive or relentless, such as, jaundice, bleeding tendencies, abdominal pain, vomiting, impaired appetite, weakness, weight loss, and, in some cases, hypersplenism. Portal hypertension and ascites also occur as in patients with portal cirrhosis. Clinically, there may be no difference between posthepatitic portal cirrhosis and postnecrotic cirrhosis, although pathologically they are distinct.[43,44,65] So confusing and obscure was the definition of postnecrotic cirrhosis that eight pathologists participated in a Conference on Liver Injury at the Sixth Conference of the Josiah Macy, Jr. Foundation on May 1, 1947, and attempted to arrive at a morphological explanation.[16] These authorities agreed on complete histological recognition in only 19 out of 106 cases of postnecrotic cirrhosis. When additional information regarding gross description of the liver and clinical data was added, the incidence of agreement increased to 35 out of 106 cases. As has been concluded, interpreting sufficiently large microscopic sections of postnecrotic cirrhosis is mandatory to adequately diagnose this condition. Generally, the histological recognition of postnecrotic cirrhosis is not reliable when small sized specimens of a needle biopsy of the liver are employed. The clinical picture of postnecrotic cirrhosis also is frequently indistinguishable from portal or even primary bi-

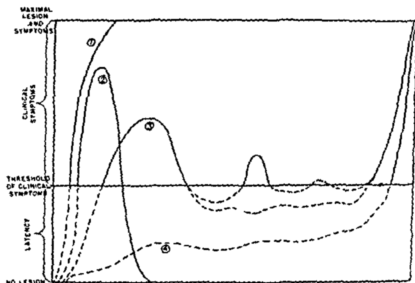
rhosis has also been attributed to a number of hepatotoxic agents such as *phosphorus, carbon tetrachloride, chloroform, cincophen,* trinitrotoluol, organic hair dye, naphthalene, mushroom poisoning, paradichlorobenzene and arsenic.[8,12,22,41,42,47,56,57,65,70-84,91,92,84,85,89,90] It has been demonstrated that viral hepatitis usually subsides without sequelae, but may progress to a subacute or chronic hepatitis or various types of cirrhosis including the postnecrotic variety.[4,90] The incidence of cirrhosis following serum hepatitis is unknown. However, it is recognized that serum hepatitis occurs after transfusions of pooled plasma in 5 to 15 per cent of cases and after transfusions of blood in less than 1 per cent.[1] In many cases of postnecrotic cirrhosis where the pathogenetic factor is obscure, it is conceivable that the patient may have been exposed to anicteric viral hepatitis or possibly some other viral disease, often unrecognizable. The severity of an attack of viral hepatitis is the sole determinant of subsequent development of cirrhosis. There are other conditions that appear to explain postnecrotic cirrhosis. These are susceptibility of the host or liver, virulence of the virus, physical condition of the patient, occurrence during the menarche, menopause or pregnancy, and, principally, insufficient medical treatment and convalescence.

The etiological factors in 60 cases of a postnecrotic cirrhosis series are listed in Table I. The relatively high incidence of antecedent jaundice (hepatitis?) is apparent. Phosphorus in the form of roach powder and carbon tetrachloride, respectively, ingested with suicidal intent were pathogenetic factors in two cases. Ratnoff and Patek studied a series of 45 cases of postnecrotic cirrhosis.[77] Thirteen patients were chronic alcoholics, 12 had had infectious hepatitis, 6, an attack of acute hepatitis from five to twelve years before clinical cirrhosis, 4, arsenical therapy for syphilis and 1, exposure to other hepatotoxic drugs. An antecedent history of cincophen therapy, hyperthyroidism, brucello-

TABLE I
ETIOLOGICAL FACTORS IN POSTNECROTIC CIRRHOSIS
(60 cases)

Jaundice (hepatitis)	27 cases	(45%)
Carbon tetrachloride	1 case	(1.7%)
Phosphorus	1 case	(1.7%)
Cryptogenic	31 cases	(51.6%)

degeneration, and rarely, the de Toni-Fanconi syndrome. Chronic alcoholism and malnutrition, abbreviated convalescent management of viral hepatitis, especially during the menarche, pregnancy and menopause have been considered to be contributing etiological factors It is generally recognized that viral hepatitis may progress to cirrhosis as originally postulated by Jones and Minot in 1923, and may be portal, postnecrotic or possibly primary biliary (cholangiolitic) in type [3,4,11,19,27,29,33,39,43,44,48,50,52,57,60,69,71,78,84,91,93]



Variations in the course of hepatitis (1) Acute hepatitis progressing rapidly to death. (2) Acute hepatitis with recovery (3) Acute hepatitis with apparent recovery but actually transition to latent stage which with or without remissions eventuates in advanced cirrhosis (4) Hepatitis latent from the start until advanced liver insufficiency supervenes

Fig 1 (Courtesy, Bloomfield, A—Am J M Sc—1938)

These investigators have demonstrated that postnecrotic cirrhosis is a sequelae of infectious or serum hepatitis Reliable evidence of this morphological transition is derived from serial needle biopsies of the liver supplemented by a presumptive history of previous hepatitis. Postnecrotic cirrhosis may indicate not only a progressive, unremitting parenchymal hepatic disease but may represent recrudescence of hepatitis followed by a relatively static course progressing to cirrhosis (Fig. 1).[13,20,63,88] Postnecrotic cir-

of cirrhosis. (8 36 per cent). Postnecrotic cirrhosis occurs in more females than males in a ratio of 2:1 and affects younger age groups more frequently than portal cirrhosis.[3 7 47 51 56 71 73 86] In Mallory's cases of postnecrotic cirrhosis, there were 29 males and 17 females.[54 57] Bjorneboe and Raaschou described 108 patients in Denmark with subacute atrophy of the liver of which 6 were men and 102 were women.[11] The predominant age range for females was between the sixth and eighth decades In the current series of cases, there were 12 females in the second decade, 5 in the third, 2 in the fourth, 9 in the fifth, 12 in the sixth, 5 in the seventh, and 1 in the eighth This suggests that, in females, postnecrotic cirrhosis is the most prevalent during the periods of menarche and menopause.[17 45] The series of postnecrotic cirrhosis reported by Ratnoff and Patek, however, did not disclose such an age distribution.[73] Postnecrotic cirrhosis is one of the most common pathological types of cirrhosis observed in infants and children (Chapter 12).[12 79 81] A marked incidence of postnecrotic cirrhosis has been reported among women in their postmenopausal period.[11 38] Of 124 cases of epidemic hepatitis in Copenhagen in 1941-45, all but 1 case was a female Seventy-nine per cent occurred above fifty years of age with a mortality of 61 per cent, a long preicteric phase in 64 per cent of cases, and an average duration of nine months in fatal cases Hepatitis which occurs during pregnancy has a poor prognosis and, in rare instances, may lead to postnecrotic cirrhosis Frucht and Metcalfe studied 11 women who had had infectious hepatitis during pregnancy one to eighteen years previously.[29] Only two were free of clinical and laboratory evidence of hepatic disease, suggesting that the concurrence of infectious hepatitis and pregnancy, particularly in the last trimester carries a high morbidity and marked tendency to chronic liver damage

PATHOLOGICAL FEATURES

The pertinent data of a series of necropsy cases of postnecrotic cirrhosis can be found in Table II This should be compared with similar data of other types of cirrhosis already mentioned It becomes obvious then that the liver of postnecrotic cirrhosis has particularly impaired hepatic resource and is unable to with-

sis and infantile diarrhea occurred in another series of patients with postnecrotic cirrhosis.[83]

In 60 cases of postnecrotic cirrhosis studied at necropsy, antecedent jaundice was present in 7 cases, jaundice within six months of death in 3 cases, and jaundice for a period exceeding six months from the time of death in 17 cases. Baggenstoss and Stauffer studied 43 cases of posthepatitic cirrhosis which included 30 cases of postnecrotic cirrhosis.[4] Antecedent jaundice occurred in 7 cases, jaundice within six months of death in 21 cases and jaundice more than six months prior to death in 13 cases. Therefore, it appears that viral hepatitis may progress quickly to postnecrotic cirrhosis, or a prolonged latent period may supervene.[11,19,23,27,38,39,48,50,52,65,66] Howard and Watson found that the antecedent jaundice occurred in 33 per cent and alcoholism in 22 per cent of 100 cases of cirrhosis.[37] The interval between viral hepatitis and symptomatic cirrhosis is irregular, too prolonged or unpredictable usually to establish chronologically a clinical sequence. It is not surprising that many patients forget a past acute febrile illness with minimal jaundice occurring several years before developing cirrhosis. Low grade jaundice may be obscured by fluorescent or poor lighting or cosmetics. In several instances, patients with postnecrotic cirrhosis have at a later date recalled an antecedent illness suggestive of acute hepatitis. Sporadic anicteric hepatitis has been reported with symptoms of upper respiratory infection, fatigue, fever, hepatosplenomegaly, pharyngitis and lymphadenopathy.[15,21,85] It is conceivable that many instances of cryptogenic cirrhosis may have been produced by an attack of anticteric hepatitis. Klatskin recently reported 12 cases of postnecrotic cirrhosis (10 females and 2 males) during an eight-year period as the sequela of anicteric viral hepatitis.[48a] These patients had initial constitutional and gastrointestinal complaints. Early postnecrotic cirrhosis developed following an attack of acute fulminant hepatitis early in the third trimester of gestation in one patient.

INCIDENCE

The incidence of postnecrotic cirrhosis as compared to all other types of cirrhosis varies 5 to 37.5 per cent.[43] Mallory reported 46 cases of postnecrotic cirrhosis in 550 cases of all types

of cirrhosis (8.36 per cent). Postnecrotic cirrhosis occurs in more females than males in a ratio of 2:1 and affects younger age groups more frequently than portal cirrhosis [3,7,47,51,54,71,73,84]. In Mallory's cases of postnecrotic cirrhosis, there were 29 males and 17 females [54,57]. Bjørneboe and Raaschou described 108 patients in Denmark with subacute atrophy of the liver of which 6 were men and 102 were women [11]. The predominant age range for females was between the sixth and eighth decades. In the current series of cases, there were 12 females in the second decade, 5 in the third, 2 in the fourth, 9 in the fifth, 12 in the sixth, 5 in the seventh, and 1 in the eighth. This suggests that, in females, postnecrotic cirrhosis is the most prevalent during the periods of menarche and menopause.[17,45] The series of postnecrotic cirrhosis reported by Ratnoff and Patek, however, did not disclose such an age distribution [73]. Postnecrotic cirrhosis is one of the most common pathological types of cirrhosis observed in infants and children (Chapter 12).[12,29,91] A marked incidence of postnecrotic cirrhosis has been reported among women in their postmenopausal period [11,35]. Of 124 cases of epidemic hepatitis in Copenhagen in 1944-45, all but 1 case was a female. Seventy-nine per cent occurred above fifty years of age with a mortality of 61 per cent, a long preicteric phase in 64 per cent of cases, and an average duration of nine months in fatal cases. Hepatitis which occurs during pregnancy has a poor prognosis and, in rare instances, may lead to postnecrotic cirrhosis. Frucht and Metcalfe studied 11 women who had had infectious hepatitis during pregnancy one to eighteen years previously [28]. Only two were free of clinical and laboratory evidence of hepatic disease, suggesting that the concurrence of infectious hepatitis and pregnancy, particularly in the last trimester, carries a high morbidity and marked tendency to chronic liver damage.

PATHOLOGICAL FEATURES

The pertinent data of a series of necropsy cases of postnecrotic cirrhosis can be found in Table II. This should be compared with similar data of other types of cirrhosis already mentioned. It becomes obvious then that the liver of postnecrotic cirrhosis has particularly impaired hepatic resource and is unable to with-

TABLE II

PERTINENT NECROPSY DATA IN 60 CASES OF POSTNECROTIC CIRRHOSIS

Weight of liver	
Largest, gm	2,520
Smallest, gm	711
Mean Weight, gm	1,210
Weight of spleen	
Largest, gm	830
Smallest, gm	200
Mean Weight, gm	485
Esophageal varices	42
Ruptured	28
Hemorrhagic gastritis	9
Ascites	39
Hydrothorax	22
Bronchopneumonia	37
Hepatoma	1

stand stress in comparison to the other types of cirrhosis. Postnecrotic cirrhosis has been described in several pathological studies.[4, 11, 45, 73, 78, 79, 84] The histogenesis of postnecrotic cirrhosis has been reconstructed in Chapter 3. Baggenstoss and Stauffer reported 30 cases of postnecrotic cirrhosis of which 9 cases were described as the lobar type.[4] Fifteen of sixty cases met this morphological criterion in the current series. The lobar type of postnecrotic cirrhosis is characterized by very large, irregular regenerative nodules, broad zones of deeply indented fibrous connective tissue, marked hepatic atrophy, and a mean weight of 1,163 gm. (Fig. 2). In this group, atrophy of the left lobe of the liver occurs frequently, and the livers resemble hepar lobatum. Bergstrand noted the lobar type of postnecrotic cirrhosis as a sequela of the Swedish epidemic of infectious hepatitis in 1927.[9] Baggenstoss and Stauffer remark that this type of postnecrotic cirrhosis suggests a severe antecedent attack of infectious hepatitis with vigorous nodular regeneration, and that atrophy of the left lobe of the liver is best explained by the "streamline" phenomenon of portal blood flow. The latter concept was originally conceived by Copher and Dick in 1928 to explain the normal mechanism, i.e., the right lobe of the liver receives nutritious portal blood from the superior mesenteric vein and the left lobe blood predominantly from the splenic vein.[18, 31] In 7 of 9 cases of the



FIG 2 Postnecrotic cirrhosis, lobar type of regenerated nodule Atrophy of left lobe of liver, weight 660 gm , death from hepatic insufficiency

lobar type of postnecrotic cirrhosis described by Baggenstoss and Stauffer, atrophy of the left lobe of the liver was present [4]

The nodular type of postnecrotic cirrhosis was present in 45 cases of the current series and in 21 of 30 cases reported by Baggenstoss and Stauffer (Fig 3) Actually, this gross hepatic morphological type is a compromising morphological group between the lobar type and granular (portal) type of cirrhosis The mean weight of the liver was 1,079 gm The latter gross morphological appearance is indistinguishable from portal cirrhosis, whereas the nodular variety represents larger, irregular regenerative nodules separated from one another by broad areas of fibrous connective tissue Consequently, gross distinction between portal and postnecrotic cirrhosis is not difficult except in borderline cases The distinction between these morphological types of postnecrotic cirrhosis has empirically clinical limitations.

Baggenstoss and Stauffer and participants in the Conference on Liver Injury, May 1, 1947, at the Sixth Conference of the Josiah Macy, Jr Foundation, described the histological criteria



FIG. 3 Postnecrotic cirrhosis, nodular type Female, nine years old, regenerative nodules measuring 1.5 cm diameter, atrophic liver, weight 0.8 gm (Kleckner, M. S., Jr — South M J — Jan., 1957)

of postnecrotic cirrhosis as follows the hepatic cells in the regenerative nodules disclose frequent bizarre forms, slight or absent fatty infiltration, rare alcoholic-hyaline cytoplasmic bodies, moderate to severe focal necrosis, and round cells; the internodular stroma is represented by connective tissue consisting largely of collapsed reticulum framework, reduplication of the bile ducts, and infiltration of round cells; and compression, distortion and inflammation of the larger intrahepatic veins are present (Figs. 4, 5).[4 16] Many pathologists feel that needle biopsy of the liver is an unreliable method for the histological diagnosis of postnecrotic cirrhosis. However, if a sufficient core of hepatic tissue is obtained by the Stauffer modification of the Vim-Silverman

needle or the Terry aspirating needle, which obtain a specimen of liver ranging from 2.5 to 1.0 cm. in length, the histologic diagnosis of postnecrotic cirrhosis is possible. Such a biopsy may include, particularly, the large regenerative nodules of the nodular type of postnecrotic cirrhosis. Nevertheless, one still encounters the problem in the same patient of unquestionable histological diagnosis of portal cirrhosis by needle biopsy and postnecrotic cirrhosis at gross examination. It is generally impossible to identify the lobar type of postnecrotic cirrhosis by liver biopsy because of the massive size of the regenerative nodules and marked atrophy of the liver.

CLINICAL FEATURES

The incidence of the initial clinical manifestations in 60 cases of postnecrotic cirrhosis is listed in Table III. Ratnoff and Patek noted that the initial symptoms and signs of postnecrotic



FIG. 4. Postnecrotic cirrhosis, needle biopsy of liver at necropsy. Hepatocellular necrosis, bile duct proliferation, extensive round cell infiltration especially in the stroma, distorted architecture and fibrosis; note that the actual size of the regenerative nodules is incompletely obtained in the specimen. (H. & E., X 100.)



FIG. 3 Postnecrotic cirrhosis, nodular type Female, nine years old, regenerative nodules measuring 1.5 cm diameter, atrophic liver, weight 68 gm (Kleckner, M S, Jr—South M J—Jan, 1957)

of postnecrotic cirrhosis as follows: the hepatic cells in the regenerative nodules disclose frequent bizarre forms, slight or absent fatty infiltration, rare alcoholic-hyaline cytoplasmic bodies, moderate to severe focal necrosis, and round cells; the internodular stroma is represented by connective tissue consisting largely of collapsed reticulum framework, reduplication of the bile ducts, and infiltration of round cells; and compression, distortion and inflammation of the larger intrahepatic veins are present (Figs. 4, 5).[4 16] Many pathologists feel that needle biopsy of the liver is an unreliable method for the histological diagnosis of postnecrotic cirrhosis However, if a sufficient core of hepatic tissue is obtained by the Stauffer modification of the Vim-Silverman

needle or the Terry aspirating needle, which obtain a specimen of liver ranging from 2.5 to 1.0 cm. in length, the histologic diagnosis of postnecrotic cirrhosis is possible. Such a biopsy may include, particularly, *the large regenerative nodules of the nodular* type of postnecrotic cirrhosis. Nevertheless, one still encounters the problem in the same patient of unquestionable histological diagnosis of portal cirrhosis by needle biopsy and postnecrotic cirrhosis at gross examination. It is generally impossible to identify the lobar type of postnecrotic cirrhosis by liver biopsy because of the massive size of the regenerative nodules and marked atrophy of the liver.

CLINICAL FEATURES

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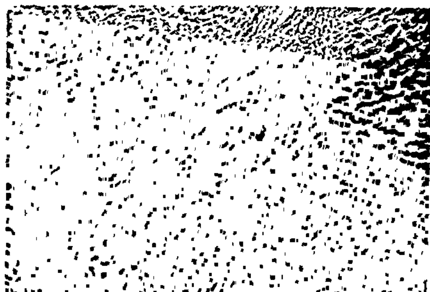


Fig. 5 Postnecrotic cirrh[illegible] stroma with round cell infiltration, reticulum [illegible] soids, displacement of the central veins by reticulum collapse and [illegible] necrosis. This is a wedge hepatic biopsy specimen obtained at the time of splenectomy and splenorenal shunt for hypersplenism and bleeding esophageal varices. A battery of hepatic function tests were normal except for a 6 per cent retention of BSP. Grossly, the liver suggested postnecrotic cirrhosis (nodular type). (H & E, ×60)

TABLE III
INCIDENCE OF INITIAL CLINICAL
MANIFESTATIONS IN POSTNECROTIC CIRRHOSIS

(22 Males, 48 Females. Youngest Age, 11. Oldest Age, 72. Mean Age, 42)

	(60 cases)	*Ratnoff & Patek (45 cases)*
Initial manifestation	*(%)*	*(%)*
Jaundice	43	22
Abdominal pain	30	13*
Edema	22	9
Gastrointestinal hemorrhage	13	(2 cases)
Ascites	6	11†
Fever	5	(1 case)
Nausea and vomiting	3	7
Anorexia	—	24
Onset Resembling Hepatitis	—	27

*Epigastric distress
†Swollen abdomen

cirrhosis were acute or suggestive of viral hepatitis, i.e., anorexia, loss of weight, jaundice, dark urine, light stools, fever, malaise, nausea, vomiting, and abdominal pain, or symptoms with an insidious onset such as ascites, edema, weakness or loss of weight and abdominal pain.[33] The major initial symptoms of 43 cases of posthepatitic cirrhosis (30 cases of postnecrotic cirrhosis) reported by Baggenstoss and Stauffer were ascites in 3 and jaundice in 35 instances.[4]

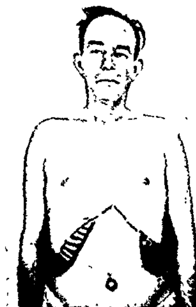


FIG. 6. A patient with postnecrotic cirrhosis. He related a history of antecedent viral hepatitis and/or carbon tetrachloride exposure four years ago, enlargement of liver and spleen, pectoral alopecia, umbilical hernia, spider angioma, and malnutrition; his principal complaints were abdominal pain and weakness. Hypersplenism was confirmed, and histological examination of the biopsy of the liver suggested postnecrotic cirrhosis.

The eventual symptoms found in a series of patients with postnecrotic cirrhosis are listed in Table IV. Abdominal pain and weakness are the most common symptoms. Abdominal pain may vary in character and pattern, being described as discomfort,

TABLE IV
INCIDENCE OF EVENTUAL SYMPTOMS IN POSTNECROTIC CIRRHOSIS

Symptom	(60 cases) (%)	*Ratnoff & Patek* (45 cases) (%)
Weakness	100	31
Abdominal pain	71	80
Bleeding tendency	55	10
Menstrual abnormality	37	36
Gastrointestinal hemorrhage	30	37
Dyspnea	28	—
Constipation	24	13
Pruritus	15	16
Diarrhea	12	29
Nausea	12	47
Vomiting	12	33
Anorexia	—	58
Weight Loss	—	40
Drowsiness	—	11

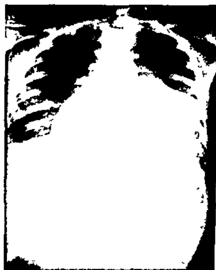



FIG. 7a Roentgenogram disclosing massive sanguinous pleural and pericardial effusion and ascites in a patient with postnecrotic cirrhosis Marked cardiac tamponade occurred.

FIG 7b Same case following cardiac paracentesis and thoracentesis Patient died there months later from hepatic insufficiency

pleuritic or colicky, and located in the epigastrium or right subcostal area, often radiating to the right shoulder or even contralaterally. Because jaundice and abdominal pain occur as predominant symptoms, patients have been subjected to needless

and even fatal abdominal exploratory operations Yazigi and his associates found abdominal pain in 6 of 9 patients with postnecrotic cirrhosis and Baggenstoss and Stauffer in only 6 of 13 patients with the same condition [6,22] Table IV discloses complaints in patients with postnecrotic cirrhosis referable to the gastrointestinal tract. These are constipation, diarrhea, vomiting, indigestion, anorexia, pruritus, loss of weight, weakness and abdominal distention

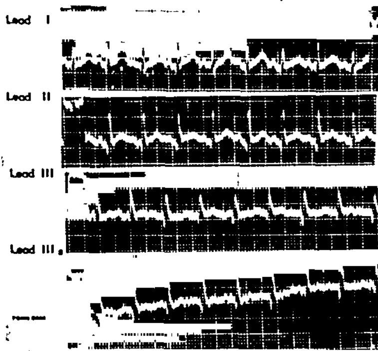


Fig 7c Electrocardiogram of same showing effects of a sanguinous pericardial effusion (tamponade) and tachycardia

The incidence of physical findings in the current series and those of Ratnoff and Patek are present in Table V (Fig 6). On the basis of physical signs alone, there is only slight dissimilarity between postnecrotic cirrhosis and portal cirrhosis other than

TABLE V
INCIDENCE OF PHYSICAL FINDINGS IN POSTNECROTIC CIRRHOSIS

Physical Signs	*(60 cases)* (%)	*Ratnoff & Patek (45 cases)* (%)
Enlarged liver	73	76
*Enlarged spleen	71	42
Esophageal varices	63	—
Jaundice	59	89
Edema	51	71
Ascites	40	92
Fever	40	40
Spider angioma	37	22
Ecchymosis	. 30	—
Palmar erythema	26	16
Loss of hair	17	—
Hemorrhoids	17	33
Striae	13	—
Testicular atrophy	7	—
Gynecomastia	6	—
Clubbed fingers	5	—
Cutaneous melanosis	5	6
Acne	—	20
Hydrothorax	—	27

the incidence of jaundice, splenomegaly, fever and spider angioma, which is more common in the former Jaundice is usually regarded as a common early manifestation in postnecrotic cirrhosis and as a terminal finding or transient hepatic insufficiency in portal cirrhosis Massive gastrointestinal hemorrhage, bleeding tendencies such as metromenorrhagia, ecchymosis, petichiae, hematuria, bleeding gums, purpura and epistaxis occur frequently in this condition Bleeding tendencies were found in 13 of 43 cases of posthepatitic cirrhosis by Baggenstoss and Stauffer, Massive ascites, bilateral pleural effusion, and pericardial effusion, sanguinous in nature, were present during the terminal clinical course in one patient recently observed (Fig 7a, b, c).

POSTNECROTIC CIRRHOSIS IN YOUNG FEMALES

An obscure, intriguing condition usually associated with postnecrotic cirrhosis has been described in young girls (Fig 8a, b) *Arthritis, fever, skin rash, features of Cushing's disease and lupus* erythematosus, bleeding tendencies, hepatic insufficiency, hypersplenism and marked hypergammaglobulinemia, acne, edema, and menstrual abnormalities are the main clinical features of this variety of cirrhosis (Fig. 9).[14 34 43 46 51 55] Bearn, Kunkel and Slater



Fig 8a Postnecrotic cirrhosis nodular type Twenty-one year old female with hypergammaglobulinemia, clinical features of Cushing's disease and severe hypersplenism, weight, 1,250 gm death was caused from hepatic insufficiency (Kleckner, M S Jr —South M J —1957)

Fig 8b Sagittal section of same case

have reported 23 patients of this type.[7] They found the average duration of the disease to be seven years. In the majority of cases it was considered cryptogenic. They emphasize the systemic nature of this condition. Matteini reported the high incidence of hepatic dysfunction in women with *menstrual irregularities*.[59] *Because* plasma L.E. cells may be demonstrated in cirrhosis, it has been termed "lupoid hepatitis."[85] This suggests a relationship, rather than concurrence, between postnecrotic cirrhosis and disseminate lupus erythematosus or biologically false-positive plasma L.E. cells.[10,33,40,51,55,61] The association of disseminate lupus erythematosus and cirrhosis, on the other hand, is rare.[32,45,61] Three young girls with an active postnecrotic cirrhosis were observed recently with fatigue, physical appearance of Cushing's disease, fever, *arthralgia, bleeding tendencies, amenorrhea, hypersplenism, ascites* and edema. Laboratory findings disclosed marked hypergammaglobulinemia, high erythrocyte sedimentation rate, markedly abnormal values of cephalin-cholesterol flocculation, thymol turbidity and zinc sulfate turbidity test, elevated serum transaminase and serum iron, low serum cholinesterase and hypoprothrombinemia. Hepatic insufficiency, hypersplenism and features of Cushing's disease in these instances respond inconsistently to the conventional management of postnecrotic cirrhosis. The urinary 17-ketosteroids in two patients were normal, the urinary *corticoid* values were elevated and the plasma L. E. test was positive. The urinary excretion of reducing corticoids is particularly elevated in this group.[14,51] The therapeutic use of a corticosteroid medication in postnecrotic cirrhosis frequently produces marked chemical improvement.

LABORATORY FINDINGS

The salient laboratory findings in 60 cases of postnecrotic cirrhosis are listed in Table VI. This emphasizes that leucopenia, normocytic anemia, thrombocytopenia, hypoalbuminemia with hyperglobulinemia, markedly abnormal hepatic flocculation tests and decreased plasma cholesterol and cholesterol esters occur persistently and abnormally in patients with postnecrotic cirrhosis. *An inactive* postnecrotic cirrhosis may occur as was demonstrated in the case of a young girl with minimally abnormal hepatic

flocculation tests and a normal bromosulfathalein retention in forty five minutes. The results of plasma electrophoresis in cases of postnecrotic cirrhosis are listed in Chapter 16 While this test is

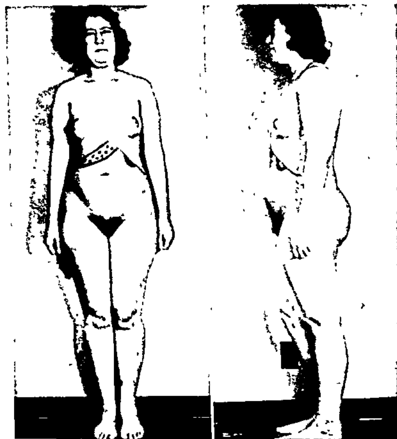


FIG 9a. Postnecrotic cirrhosis in nineteen year old female with ascites, edema and 9b rheumatoid like arthritis, amenorrhea, fever, full blown features of Cushing s disease, hepatosplenomegaly, acne, (Hgb 7 1 gm per 100 cc, RBC 3 930,000 per cu mm, WBC 5,100 per cu mm platelets 152,000 per cu mm, direct/total serum bilirubin, 1 41/3 26 mg per cent, B SP 46% $ZnSO_4$ turbidity 28 2 S H units, thymol turbidity 16 2 units, CCF 4+, transaminase (SGO T) 1192, cholinesterase 0 19 ∠ ph A G 1 8 4 7 gm per 100 cc, prothrombin time 36 per cent)

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TABLE VII

Causes of Death in 60 Cases of Postnecrotic Cirrhosis

Immediate	*Cases*
Hepatic insufficiency	28
Bleeding esophageal varices*	19
Hepatoma	1
Hemorrhagic gastroenteritis	4
Intestinal obstruction	1
Pneumonia	4
Rupture aneurysm of portal vein	1
Pyelonephritis	1
Suicide	1
Contributory	
Pneumonia	14
Postoperative shock	9
Thrombosis of portal vein	5
Gastric ulcer, benign	2
Carcinoma of breast	1
Cellulitis	1
Congestive heart failure	1

*In most instances this induced fatal hepatic coma

This condition is a manifestation of portal hypertension and, therefore, is often associated with esophageal varices. Many cases of splenic anemia, originally described by Gretsel in 1866 and termed Banti's syndrome in 1882, have been considered to be cirrhosis with portal hypertension and a secondary hypersplenic state [5,30] In the current series of postnecrotic cirrhosis, hypersplenism was present in 47 per cent, splenomegaly in 71 per cent, and esophageal varices in 63 per cent. Cirrhotics with hypersplenism are extremely susceptible to infections. These patients have poor bodily resistance to infection. They easily succumb to bronchopneumonia, generalized staphylococcemia or other bacterial infections (Table VIII).

PRINCIPLE AND CONTRIBUTING CAUSES OF DEATH

The immediate and contributory causes of death in 60 cases of postnecrotic cirrhosis are listed in Table VII (Figs. 10, 11, 12). In the series of 15 cases of postnecrotic cirrhosis reported by Ratnoff and Patek, hepatic insufficiency was responsible for death in 27 cases, gastrointestinal hemorrhage in 13 cases, peritonitis in 7 cases, pneumonia in 5 cases, renal insufficiency in 3 cases and congestive heart failure in 2 cases.[47,53] Four of their patients died postoperatively; in three instances death was due to

TABLE VI

LABORATORY DATA IN 60 CASES OF POSTNECROTIC CIRRHOSIS

Laboratory Data	*Number of Cases*
Leucopenia	29
Leucocytosis	6
Thrombocytopenia	39
Normochromic, normocytic anemia	17
Hypochromic, microcytic anemia	11
Hyperchromic, macrocytic anemia	7
Hemolytic anemia	21
[illegible]	34
[illegible]	18
[illegible]	42
[illegible]	52
[illegible]	17 (18 cases)
[illegible]	27
[illegible]	12 (15 cases)
Low serum cholinesterase	9 (13 cases)
Hypoprothrombinemia	46
False positive blood serology	2
Low cholesterol–cholesterol esters	15 (22 cases)
Average BSP determination 45 minutes	31%
Average sedimentation rate (Westergren)	41
Average direct and indirect serum bilirubin	2 4 — 3 7

not diagnostic hypergammaglobulinemia has been noted more frequently in postnecrotic cirrhosis than in any other type of cirrhosis These laboratory findings suggest, in general, that the clinical picture of postnecrotic cirrhosis is predominated by hepatic insufficiency whereas portal cirrhosis is usually characterized by manifestations of portal hypertension and water retention As Baggenstoss has postulated, the smaller regenerative nodules characteristic of portal cirrhosis compress significantly the small hepatoportal venules, and this feature may explain the higher incidence of portal hypertension in patients with portal cirrhosis[3] Hypersplenism or congestive splenomegaly is frequently observed in patients with posthepatitic portal cirrhosis or postnecrotic cirrhosis and splenomegaly[20 24 26 35 62 56] This condition occurred in 37 per cent of the current series The laboratory manifestations of hypersplenism which are observed wholly or in part include leukopenia, lymphocytosis, thrombocytopenia, normocytic anemia, reticulocytosis, elevation of the indirect serum bilirubin, normoblastic hyperplasia of the bone marrow, increased fecal and urinary urobilinogen, and hemosiderosis of the liver and spleen

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TABLE VIII
CLINICAL COURSE AND LABORATORY DATA OF A FIFTY-SIX-YEAR OLD MALE WITH POSTNECROTIC CIRRHOSIS AND HYPERSPLENISM
(SUSPECTED INFECTIOUS HEPATITIS IN 1928)

	Year			
Clinical Manifestation	*1953*	*1954*	*1955*	*1956*
Body weight, lbs	170	169	187	199
Emaciation	o	+	+	o
Jaundice	+	o	+	o
Ascites	o	o	o	o
Edema	o	+	+	o
Alopecia	o	+	+	+
Palmar erythema	o	o	o	+
Testicular atrophy	o	o	o	+
Hepatomegaly	o	4f	3f	3f
Splenomegaly	2f	6f	6f	4f
Laboratory Data	3.6	0.2	0.2	0.4
	—	—	—	—
Bilirubin serum D. I., mg. per 100 cc	4.2	1.05	1.2	1.6
Alk. phosphatase, Bodansky units	—	—	4.4	3.3
BSP retention % 45 min	—	26	31	11
Cephalin floc. 48 hrs	4+	4+	4+	3+
Cholesterol	178	172	167	231
Thymol turbidity, units	67	100	100	100
Prothrombin time %	o	o	o	o
Esophageal varices (endoscopically)	11.5	13.9	11.5	11
Hemoglobin, gm. per 100 cc	—	425	475	410
RBC cu. mm. x10⁴	5200	4000	5000	6800
WBC cu. mm	275,000	350,000	237,000	350,000
Platelets, cu. mm	—	52	30	41
Sedimentation rate (Westergren)	3.4	3.4	3.7	3.2
Albumin gm. per 100 cc	—	—	—	—
Globulin gm. per 100 cc	3.4	3.8	3.5	3.5

Treatment: 150 gm. protein, 100 gm. carbohydrate, fat ad lib. diet and vitamins.

hepatic insufficiency, and in one, bronchopneumonia and acute parotitis. Twenty-six of thirty cases of postnecrotic cirrhosis reported by Baggenstoss and Stauffer died from hepatic insufficiency, 5 from bleeding esophageal varices and 8 from congestive heart failure.[4] Hepatoma complicating postnecrotic cirrhosis, often as a sequela of viral hepatitis, has been reported by Mallory in 3 of 46 cases, by Baggenstoss and Stauffer in 1 of 45 cases and by Bjørneboe and Raaschou in 5 of 28 cases.[4,11,56,57,77] An unusually high incidence of benign gastric ulcer (10.2 per cent) occurred in their series of postnecrotic cirrhosis (Table IX).

FIG. 11. Aneurysmal connection between right portal vein and common bile duct causing a hemocholecyst and death from massive gastrointestinal hemorrhage in case of postnecrotic cirrhosis (courtesy, Barzilai, R., and Kleckner, M. S., Jr.—Arch. Surg.—April, 1956).

Fig. 10a. Distal esophagus with collapsed varices in a case of postnecrotic cirrhosis. Death resulted from an exsanguinating hemorrhage due to a peptic (?) erosion of an esophageal varix 7 cm. from esophagogastric junction.

Fig. 10b. Esophagogram of same patient disclosing huge esophageal varices.

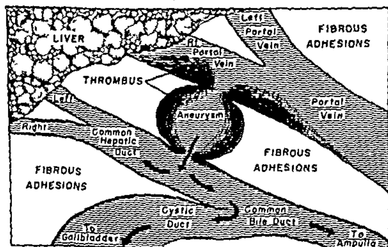


TABLE IX

CLINICAL COURSE AND LABORATORY DATA OF A TWENTY-ONE YEAR OLD MALE WITH POSTNECROTIC CIRRHOSIS

	Months Following Infectious Hepatitis					
Clinical Manifestations	*19*	*20*	*23*	*26*	*38*	*41*
Jaundice	+	o	+	o	+	Died,
Hepatomegaly	*8f*	*8f*	*10f*	*7f*	*1f*	ruptured
Splenomegaly	*2f*	*2f*	*5f*	*4f*	*5f*	*esophageal*
Ascites	o	+	o	o	o	hemorrhage
Edema	o	+	+	o	o	
Spider angioma	o	o	+	+	+	
Palmar erythema	o	o	+	o	+	
Alopecia	o	o	o	o	o	
Pruritus	+	o	o	o	+	

Laboratory Data							
	D	0 2	2 1	0 8	10 6	0 5	2 2
Serum bilirubin mg /100 cc	T	1.5	4 0	1.5	16 4	1 6	3 9
BSP retention % 45 min			36	38	45	21	48
Blood cholesterol, mg 100 cc 120 300			—	—	—	—	110
Serum albumin gm/100 cc 3 6 5 1			3.8	3.5	2 4	4 1	3 6
Serum globulin, gm/100 cc 1.5 3 1			2 4	2 3	3 7	1 8	3.5
Cephalin flocculation 48 hr 0 1+			4+	2+	4+	1+	4+
Thymol turbidity 0 7			—	18.2	7	—	16.3
Prothrombin time, % of normal 100			45	40	50	50	59
Sedimentation rate Westergren 0 10			15	22	28	1	20

Treatment 200 gm protein 500 gm carbohydrate, fat ad lib diet, Brewer's yeast vitamins 2 month ACTH Rx



PROGNOSIS

The comparative survival rates of patients having portal and postnecrotic cirrhosis during a seven year period following the first episode of jaundice, hematemesis, or ascites are illustrated in Figure 12, 13 & 14, Chapter 6. The prognosis of postnecrotic cirrhosis generally is poor. In Ratnoff and Patek's series of 45 cases of postnecrotic cirrhosis, 29 (64 per cent) survived for one year after the development of symptoms, and 10 (22 per cent) were still alive at the end of five years[32] They state that the prognosis of postnecrotic cirrhosis appeared somewhat better than portal cirrhosis This is contrary to our experience Bjorneboe and Raaschou calculated the average duration of symptoms in their cases of subacute atrophy of the liver was 8 2 months[11]

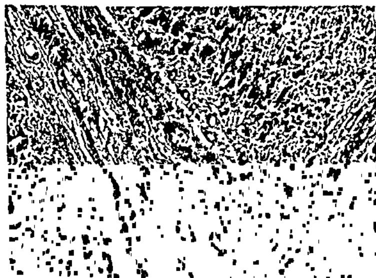


Fig 12b Surgical biopsy Hepatoma, postnecrotic cirrhosis (H & E, X60)

Fig 12a Postnecrotic cirrhosis and hepatoma Carcinomatosis, enlarged painful liver, abdominal metastases, emaciation jaundice and bleeding esophageal varices impending hepatic coma Four years previously he contracted established infectious hepatitis, following which he was incapacitated with post necrotic cirrhosis

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Chapter 8

PRIMARY BILIARY CIRRHOSIS

INTRODUCTION

PRIMARY BILIARY cirrhosis, an uncommon clinical syndrome usually observed in adult females, is characterized by chronic obstructive jaundice, acholic stools, steatorrhea, dark-colored urine, pruritus, hepatosplenomegaly, osteoporosis, osteomalacia and occasionally, xanthomatosis Hyperbilirubinemia, hyperphosphatasemia, hypercholesterolemia, hyperphospholipidemia, with patent extrahepatic biliary tract and, initially, minimal evidence of hepatocellular damage are also found The course of this condition is relentlessly progressive and is indistinguishable clinically from that of secondary biliary cirrhosis Primary biliary cirrhosis was recognized originally by Requin in 1816, Addison and Gull in 1851 and by Murchison in 1869 [1, 104, 111] As a result of studies by Hanot in 1875, "hypertrophic cirrhosis with chronic jaundice" was proposed as a new pathological entity.[53, 54] However, Hanot's criteria of this disease confused his contemporaries who had recognized only two main types of cirrhosis: Laennec's, portal cirrhosis and Charcot's obstructive biliary cirrhosis. Although the validity of Hanot's original pathological observations have been questioned lately, various descriptive and pathological terms have been employed synonymously, often compromisingly and ambiguously, to discriminate primary biliary cirrhosis from portal and secondary biliary cirrhosis [6, 46, 57, 64, 72, 73, 75, 81, 83, 94, 95, 103, 115, 116, 118, 121]

Several additional important historical landmarks pertaining to primary biliary cirrhosis were recorded prior to the publication of the classic monographs of Thannhauser and Ahrens and their co-workers, respectively, in 1938 and 1950 [6, 41, 42, 44, 56, 137] Two clinical and histological types of hepatitis were described, namely, the hepatocellular and the cholangitic or cholangiolitic forms [29, 38, 61, 62, 74-76, 87, 101, 107, 119, 119, 138, 141, 143] The transition from hepatocellu-

lar hepatitis to cholangiolitic hepatitis and cirrhosis or from cholangiolitic hepatitis to cholangiolitic cirrhosis has been demonstrated in several reports, even though the pathogenesis of the latter condition is still controversial. Watson and Hoffbauer reported 10 cases of cholangiolitic hepatitis in 1946 in which the clinical manifestations were entirely those of obstructive jaundice with little or no impairment in hepatic cell function.[146] Histologically, the hepatic cell appeared normal, at least in the early stages of the disease, and the histopathological changes were confined to the cholangioles, consisting of chronic periportal inflammation and biliary parenchymal stasis.[90-92, 113, 118, 142, 143] It has been shown since that similar clinical syndromes, rather than a specific histopathological condition of cholangiolitic hepatitis or a hepatitis with manifestations of obstructive jaundice, may be due to viral or inflammatory condition or certain icterogenic drugs.

Thannhauser and Magendantz in 1938 reported marked increase in the serum cholesterol and phospholipids (lecithin) together with clear or non-turbid serum in certain patients with primary biliary cirrhosis.[137] In association with the presence of xanthomata, this condition has been termed "xanthomatosis biliary cirrhosis." MacMahon and Thannhauser in 1949 described xanthomatous biliary cirrhosis as a clinical syndrome characterized by hepatosplenomegaly, chronic intrahepatic obstructive jaundice, skin xanthomata of the plain or tuberous variety, and extremely high values for total cholesterol and phospholipids in the serum.[92] Subsequently, xanthomatous biliary cirrhosis or biliary xanthomatosis was demonstrated to have clinical rather than pathological implications, the essential features of which are exactly the same as described by Watson and Hoffbauer.[39, 90, 142] It remained for Ahrens and his co-workers to review comprehensively the literature on primary biliary cirrhosis from 1851 to 1950. They selected 25 cases of established primary biliary cirrhosis and xanthomatosis and added 8 of their personal cases with xanthomatosis and 9 cases without xanthomatosis.

The clinical picture usually associated with primary biliary cirrhosis may be due to various other types of cirrhosis. It is of interest to note that Weir and Snell employed the term "chronic

hepatitis with jaundice" in lieu of "biliary cirrhosis"[147] They disclosed that this condition was primarily a clinical diagnosis, and that the morphological aspect of the liver was nonspecific. Consequently, the diagnosis of "primary biliary cirrhosis" usually connotes clinical rather than pathological implications

In order to understand biliary cirrhosis, the following clinicopathological classification is suggested.[6 9 26 24 30 33 35 49 60 62 61 69 72 75 83 85 91 93 94 97 100 105 115 122 124,125 131 141]

BILIARY CIRRHOSIS

Primary Biliary Cirrhosis

1 Cholangiolitic Hepatitis
2 Cholestatic Hepatitis
3 Cholangiolitic Cirrhosis ("Primary Biliary Cirrhosis").
4 Acholangitic Biliary Cirrhosis (Aplasia of intralobular bile ducts)

Secondary Biliary Cirrhosis

1 Obstruction of the extrahepatic biliary ducts (cholelithiasis neoplasm, stricture, parasites, xanthomata, and chronic cholangitis)
2 Congenital atresia of extrahepatic bile ducts.

In 1937, Klemperer reported a case of chronic intrahepatic obliterating cholangitis Clinically, this rare condition appears indistinguishable from primary biliary cirrhosis, but there was marked narrowing and obliteration of the biliary canaliculi.[74 79] Acholangiolitic or acholangitic biliary cirrhosis can be diagnosed histologically even by needle biopsy of the liver (Fig 61, Chapter XII). The evidence to date suggests there is no difference clinically and pathologically between either cholangiolitic hepatitis and cholangiolitic cirrhosis or "primary biliary cirrhosis" with one exception This is histological evidence of cirrhosis in the case of the latter. Ahrens has used the terms pre-xanthomatous stage, xanthomatous stage, to distinguish the clinical phases of primary biliary cirrhosis[6] MacMahon has listed biliary cirrhosis under five different types: obstructive, cholangitic, pericholangitic, acholangic, and fibroxanthomatous[91]

ETIOLOGY

The pathogenetic factor of primary biliary cirrhosis is actually unknown, and a discussion of etiological possibilities is purely historical and speculative. Originally, Hanot considered that catarrhal infection of the small bile ducts produced this disease.[51] The mode by which infective or toxic agents reached the liver directly from ascending infection from the duodenum or a descending cholangitis beginning in the cholangioles became controversial. Schottmuller employed the term "cholangiolitis lenta" to describe primary biliary cirrhosis in 1921, because he considered the disease a complication of a streptococcus viridans infection of the biliary tract. Fagge and Pye-Smith in 1873 independently considered the xanthomatous features of their disease due to prolonged "cholemia" [40, 41, 110] Alcoholism, malaria, heredity and endocrine factors were once considered pathogenetic factors. Hardaway in 1881 and Török in 1893 explained primary biliary cirrhosis on the basis of obliterating intrahepatic xanthomatous lesions[6] Thannhauser and Magendantz coined the term "xanthomatosis biliary cirrhosis" in 1938 and concurred in this pathogenetic conception They regarded cirrhosis as a terminal phase of xanthomatosis biliary obstruction, and the disease itself as an inborn error of cholesterol metabolism [137]

Hemochromatosis has been associated with this disease in three instances [20, 35, 137] Hanger and Gutman in 1940 described chronic intrahepatic obstructive jaundice occurring during or following arsenical therapy.[61] Chanutin and Ludewig in 1936 and Stolzer in 1950 demonstrated xanthomatosis as a complication of this therapy [22, 135] Cases of biliary cirrhosis or intrahepatic cholestasis with and without xanthomatosis due to sarcoidosis have also been described.[43, 111] Drugs such as methyltestosterone, arsphenamine, phenothiazines, para-aminosalicylic acid, thiouracil, methimazole, isonicotinic hydrazide, phenylacetyl urea, para-aminobenzyl caffeine, propylthiouracil, phenylbutazone, carbarsone and others have been demonstrated to simulate the clinical picture of primary biliary cirrhosis (Fig 1.) [7, 10, 11, 15, 18, 19, 27, 30, 37, 59, 65, 66, 77, 86, 88, 90, 105, 108, 125, 135, 140, 145, 149, 152] Needle biopsy of the liver may distinguish primary cirrhosis from chronic idiopathic jaundice



Fig 1a Chlorpromazine hepatitis, which histologically simulates chronic obstructive jaundice, needle biopsy of the liver (H & E, X80)

Fig 1b Methyl testosterone hepatitis with similar histological features Needle biopsy of the liver (H & E, X80)

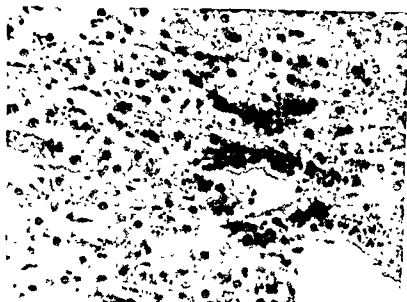


Fig 1c Dubin-Johnson syndrome or chronic idiopathic jaundice Needle biopsy of the liver Note characteristic unstainable, brown intercellular pigment Clinically, but not histologically, this condition resembles primary biliary cirrhosis (H & E X200)

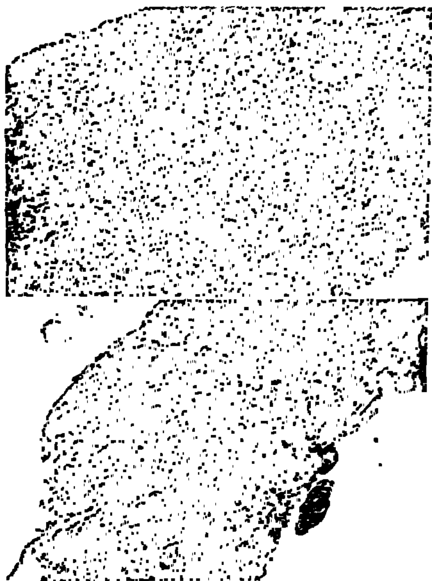
(Dubin-Johnson syndrome) [16,31,32,1-5] Chronic ulcerative colitis has been associated with this type of biliary cirrhosis [73,147] Eppinger in 1937 described two clinical and histologic varieties of hepatitis, the hepatocellular form, and the periacinar or cholangitic form The secondary form, cholangiolitic hepatitis, as Watson and Hoffbauer have demonstrated, may be caused by the virus of infectious hepatitis [142,144] They postulated that jaundice was due to leakage or diapedesis of bile, because of increased permeability of damaged cholangioles. Other investigators, however, were unable to confirm their contention of the viral etiology of this disease. Nevertheless, in the occasional case of this type, either the viral nature is very strongly suspected, or there may be a transition from viral hepatitis (hepatocellular form) to cholangiolitic hepatitis, and possibly then to cirrhosis.

In the current series of 16 cases of established primary biliary cirrhosis, there was no heredity factor, constitutional predisposi-

tion, history of antecedent infectious or serum hepatitis, known exposure to any hepatotoxic agents or therapeutic use of icterogenic drugs (Fig. 2). In all of the cases, the extrahepatic biliary system was confirmed to be patent either by direct surgical exploration, operative cholangiography or necropsy. These are unquestionably necessary procedures before a diagnosis of primary biliary cirrhosis can be established. It has been shown that the clinical picture, results of biochemical tests, needle biopsy of the liver, determination of lipid fractions in the serum, and intravenous cholangiography offer only presumptive diagnostic evidence in determining whether biliary cirrhosis is primary, and that both clinically and pathologically primary and secondary biliary cirrhosis are distinguished with difficulty. Three cases of unquestionable cholangiolitic hepatitis occurring in males for a duration of seven, fourteen and sixteen months are not included in this series. Two of these patients had infectious hepatitis with progression of the hepatocellular phase to the cholangiolitic phase and had subsequent remission without evidence of chronic hepatic damage. The third patient had serum hepatitis with manifestations of cholangiolitic hepatitis for sixteen months with eventually complete biochemical and histological hepatic remission. The 16 cases, on the other hand, demonstrated a relentless, progressive, clinical course without remission.

PATHOLOGIC FINDINGS

The paucity of pathological data, especially prior to 1945, of primary biliary cirrhosis is due to several conditions. Not only is this disease uncommon, but the pathological appearance of the liver may be indistinguishable from various stages of hepatitis, portal or postnecrotic cirrhosis, other than its greenish discoloration. Therefore, only since needle biopsy of the liver has been employed diagnostically, have the histopathological features of this condition been interpreted with certain accuracy. Serial hepatic biopsies have demonstrated the transition of a chronic pericholangitis to a biliary cirrhosis.[49, 102] However, in many cases, primary biliary cirrhosis may be underdeveloped or a final pathological stage not reached (Figs. 3a, 3b).[102] Consequently, "primary biliary cirrhosis" connotes only a clinical diagnosis. Hanot original-



FIGS 2a, b, c, d, and e Serial needle biopsies of the liver "Chronic" serum hepatitis with clinical features of chronic obstructive jaundice; clinical picture suggested transient cholangiolitic hepatitis, serial needle biopsies obtained [illegible] hepatic survey and needle biopsy of the liver implied excellent health (H & E, X80)

ly described the liver in this condition as enlarged, firm, and dark green in color. The surface of the liver in the current series of cases was fairly smooth, at most finely granular, but hob-nailed appearance of portal cirrhosis was found in some advanced cases. It is apparent that in order to understand this unusual type of cirrhosis the histopathological stages must be studied adequately by serial

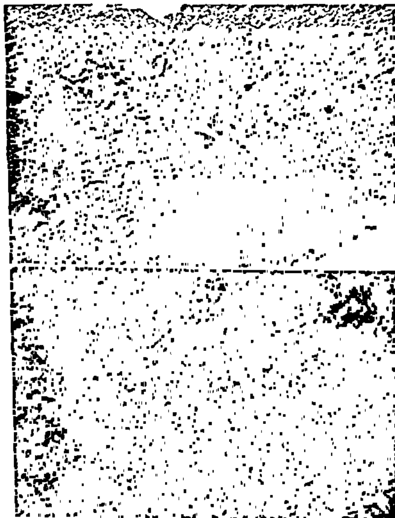


Fig. 2c and d



Fig 2e.

hepatic biopsies obtained preferably by satisfactory needle biopsies of the liver

Hepatic biopsy obtained early in this disease discloses either chronic pericholangitis with or without stasis of bile, bile thrombi in the biliary canaliculi or hepatic alterations not unlike those found in viral hepatitis as suggested by Gall (Fig. 4)[47] In several cases in the present series, an insignificant-appearing pericholangitis was the sole histological observation This histopathological feature is not infrequently demonstrated, incidentally, even in routine necropsy cases, where there is no evidence of hepatic disease. Watson and Hoffbauer noted relatively normal histological findings in some instances in the liver early in the course of cholangiolitic hepatitis and, in others, biliary stasis, multinucleated hepatic cells, and periportal fibrosis[142] MacMahon demonstrated a chronic inflammatory lesion in the interstitial portal areas in hepatic biopsies of 4 patients with the syndrome of primary biliary cirrhosis and xanthomatosis.[90] This reaction was found to have spread into the peripheral zones of the adjacent lobules, and, eventually, to obstruct biliary canaliculi, cause hepatocellular damage and collapsed many sinuses. Pro-

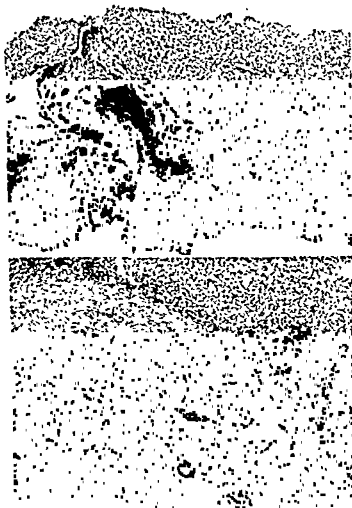


Fig. 3 Cholangiolitic hepatitis Needle biopsy of liver marked chronic pericholangitis, portal stasis of bile, parenchymal round cell inflammatory reaction, and proliferation of trabeculae into the hepatic cells, suggesting the morphological transition to cholangiolitic (primary biliary) cirrhosis (H & E, X60)

Fig. 4 Cholangiolitic hepatitis Early course of "primary biliary cirrhosis," needle biopsy of liver, this section emphasizes the extensive chronic pericholangitis with increased portal fibrous connective tissue, patent cholangioles, perilobular inflammatory reaction, the remaining parenchyma appeared relatively normal (H & E, X100)

liferation of granulation tissue, fibrosis, and nodular regeneration eventually develop. He proposed the descriptive term "pericholangiolitic biliary cirrhosis" instead of xanthomatosis biliary cirrhosis.

It has been shown that the histological features of these conditions may exist without the characteristic clinical syndrome (Fig. 1).[42,47,118,147] Gall and Braunstein studied hepatic biopsies from 14 patients with hepatitis simulating obstructive jaundice, 30 patients with ordinary viral hepatitis, and 20 patients with proven extrahepatic obstructive jaundice. The histological similarity between these two types of hepatitis was such as to suggest a close relationship (Fig. 5). A unique type of chronic intrahepatic obstructive jaundice has been described in infants and children (Chapter 12).[31,52,131] Popper and Szanto studied hepatic biopsies and autopsy specimens from patients with clinical and laboratory evidence of acute and chronic intrahepatic cholestasis in the absence of extrahepatic biliary obstruction.[109] They found that intrahepatic cholestasis is a nonspecific response of the hepatic parenchyma to injury of various types, such as viral hepatitis, portal or postnecrotic cirrhosis, icterogenic drugs, and hepatic disease with jaundice unassociated with hepatocellular damage (Figs. 6a, 6b, 6c). Consequently, they concluded that intrahepatic cholestasis could be differentiated from extrahepatic biliary obstruction only in rare instances when the latter produces hydromechanical dilatation of the bile duct, bile infarcts, and extravasation of bile into the portal tracts. Dubin states, on the other hand, that "a pathologist with considerable experience in interpreting liver biopsy specimens could probably distinguish primary cholestatic hepatitis from obstructive jaundice in about 70 per cent of cases."[30] He found bile lakes, bile granulomas and cholangitis (exudate within the lumen of intrahepatic bile ducts) only in cases of late obstructive jaundice, and irregular intralobular necrosis and fewer bile plugs in the primary variety.

This series of hepatic biopsies from patients with primary biliary cirrhosis confirms the observations of others that chronic pericholangiolitis is usually the common initial hepatic lesion in the early course of this disease regardless of the presence of

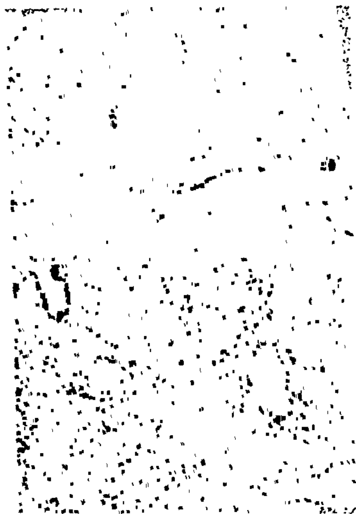


FIG 5 ... ...taneous xanthomatosis, the duration ... ...ree years Needle biopsy of liver, extension of chron... ...cholangitis into lobules, trabeculae, in a manner of producing early nodular degeneration (H & E, X60)

FIG 5b Same specimen emphasized the marked periportal fibrosis, infiltration of inflammatory cells, duplication of cholangioles and perivascular inflammation



Fig. 6a Primary biliary cirrhosis, liver weight 2,170 gm Grossly the specimen of this condition, while usually bile stained, may have a relatively smooth surface or disclose nodular regeneration *sine qua non* of cirrhosis



Fig. 6b Sagittal section of a liver from a patient with primary biliary cirrhosis (Courtesy of Hans Popper, M D)

cutaneous xanthomata, and may be associated with stasis of bile, lymphocytic infiltration, and even with mild evidence of hepatocellular necrosis (Figs. 7a, 7b). Eventually, as serial biopsies demonstrate, the histological appearance of the liver reflects an extension of the chronic pericholangitis. This inflammatory connective tissue may then expand with abundant lymphocytic infiltration peripherally to other hepatic lobules. The bile ducts in this area may be collapsed, dilated, reduplicated or inflamed. Bile thrombi may be present in the biliary canaliculi and some of the hepatic cells are stained with bilirubin. Eventually, the inflammatory connective tissue may completely surround the hepatic lobules and contain bile ducts, lymphocytes, small blood vessels, and some circumscribed hepatic cellular areas. Despite surrounding areas of inflammatory connective tissue, the hepatic lobule architecture may be preserved with the central vein intact. Hepatocellular necrosis and regeneration and lymphocytic infiltration may be present in some instances. As the disease progresses, the inflammatory connective tissue proliferates and dissects unevenly the hepatic lobules as demonstrated by Popper and Elias (Chapter 3). Progressive necrosis perpetuates during this stage. The central vein anastomosis with the portal vein, and, when nodular regeneration develops from the remaining islands of hepatic cells, biliary cirrhosis occurs (Figs. 8, 9). Whereas there are some details which obscure the morphogenesis of primary biliary cirrhosis, this condition, when fully developed pathologically, may be indistinguishable from secondary biliary cirrhosis or even portal cirrhosis. However, not all patients with this syndrome reach the pathological end-stage at which time hepatic insufficiency, ascites, and portal hypertension are present.

The gross appearance of the liver in primary biliary cirrhosis may vary. The liver may be hypertrophied, have a greenish-brown color, and may be smooth, or it may be nodular.[6, 25, 39, 58, 90–93, 113, 112] The weight of the liver in one of the three necropsy cases was 1,750 gms. and cirrhosis was present. This patient had ascites, esophageal varices, enlargement of the spleen (620 gm) and abdominal venous collateral circulation. Cirrhosis was not present in the remaining cases. In these cases, the duration of the disease

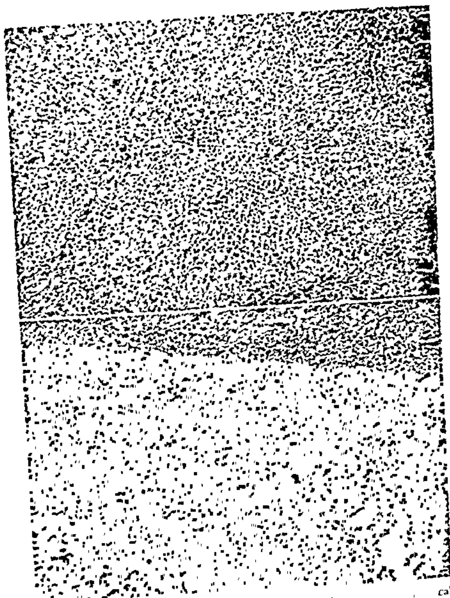


Fig 7a ... cal
duration four years, needle ... and
chronic pericholangitis, hepatic parenchyma, ... (H
& E, X80)

Fig 7b Same case one year later, needle biopsy of liver, no significant clinical change, increased amount of chronic pericholangitis with invasion into hepatic parenchyma and stasis of bile (H & E, X80) Morphologically, cirrhosis is absent



FIG 8a Primary biliary cirrhosis with cutaneous xanthomatosis Needle biopsy of the liver Clinical duration four years, chronic pericholangitis stasis of bile, hepatocellular degeneration and established cirrhosis (H & E, X80)

was six years in two cases and, in the case of the cirrhotic liver, seven and one-half years Apparently, in some cases of primary biliary cirrhosis there is no consistent correlation between the morphological appearance of the liver and the clinical or biochemical status of the patient. Cirrhosis was confirmed definitely in 6 of 17 of Ahrens' series and in two instances only six months after the onset of the disease. In patients with primary biliary cirrhosis, portal hypertension may be present without pathological evidence of cirrhosis (Table I).

CLINICAL FEATURES

The present series of cases of primary biliary cirrhosis consists of 13 women and 3 men The mean age at the onset of the disease was forty-seven years In Ahrens' series of 17 cases, all were females, and the age of most varied from seventeen to sixty-eight years in those without xanthomatosis (mean forty-five years)

TABLE I

PERTINENT NECROPSY DATA OF 5 CASES OF PRIMARY BILIARY CIRRHOSIS

Weight of liver	
Largest gm	2 730
Smallest gm	1,750
Mean weight, gm	2,275
Weight of spleen	
Largest gm	620
Smallest gm	300
Mean weight, gm	486
Esophageal varices	1
Ascites	2
Edema	3
Hydrothorax	2
Bronchopneumonia	1

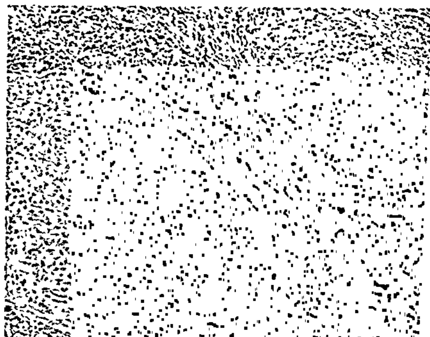


FIG 8b Same case three years later. Needle biopsy of the liver Histological evidence suggests that the regenerative nodules are granular The patient had established clinical and histological features of cirrhosis, in general. (Kleckner, M S, Jr —Ann. Int Med —June, 1954)

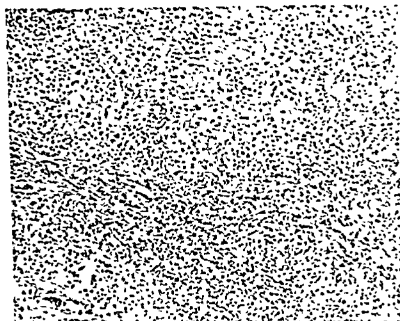


FIG. 8c Primary biliary cirrhosis Antecedent infectious hepatitis Clinical picture for five to six years of obstructive jaundice with cutaneous xanthomatosis. Needle biopsy of the liver Chronic pericholangitis, perilobular, in particular, parenchymal necrosis and stasis of bile No histological evidence of cirrhosis (H & E, X150)

and twenty-nine to fifty-one years in those with xanthomatosis (mean forty two years).

The initial symptoms of primary biliary cirrhosis are listed in Table II The most frequent initial complaints were either jaundice or pruritus in combination The insidious onset of obstructive jaundice, pruritus, anorexia, loss of weight, and diarrhea in the absence of abdominal pain or fever is occasionally observed in patients with viral hepatitis These clinical findings may prevail for six months to four years

Eventually, weakness, abdominal pain, and symptoms of chronic obstructive jaundice develop Due to impaired excretion of bile into the small intestine, patients with primary biliary

cirrhosis may have steatorrhea, flatulent dyspepsia, impaired appetite, loss of weight, intolerance to fat, bloating, nausea and vomiting (Table III). Patients often complain of back pain and, in one instance, a patient suffered fractures of the arm and hip as a result of a mild fall.

TABLE II
INCIDENCE OF INITIAL CLINICAL MANIFESTATIONS IN PRIMARY BILIARY CIRRHOSIS
(13 females, 3 males, youngest age, 27, oldest age, 69, mean age, 47)

Initial Manifestation	(16 cases) (%)	Ahrens' (17 cases) (%)
Jaundice	32	24*
Pruritus	32	55
Jaundice and pruritus	25	—
Jaundice pruritus and xanthomatosis	6	6
Xanthomatosis	6	—
Anorexia		6
Abdominal pain		6
Abdominal pain and anorexia		6
Anorexia		12
Pruritus and diarrhea		6
Diarrhea		6

*One case with melanosis

TABLE III
INCIDENCE OF EVENTUAL SYMPTOMS IN PRIMARY BILIARY CIRRHOSIS

Symptoms	(16 cases) (%)	Ahrens' (17 cases) (%)
Weakness	94	65
Pruritus	88	100
Jaundice	81	94
Abdominal pain	50	6
Bloating	50	—
Anorexia	32	23
Steatorrhea	12	59
Skeletal Pain	12	41
Gastrointestinal hemorrhage	6	35

The physical findings of primary biliary cirrhosis are listed in Table IV. These patients are generally observed in well-nourished, active women who appear slightly older than their actual age. An enlarged, smooth, nontender liver is invariably present. The size of the liver usually extends between 4 and 10 fingerbreadths below the subcostal margin along the right mid-clavicular line (Fig. 9). This finding is associated with an en-



FIG. 9a and b Primary biliary cirrhosis in a forty three year old female with xanthomatosis Serial needle biopsies of the liver demonstrated histological transition of the liver from marked pericholangitis, stasis of bile, round cell infiltration in the portal and parenchymal areas and early trabecular formation to primary biliary cirrhosis Needle biopsy of liver was performed during the eighteenth and twenty fourth month of the disease Note Figures 10 12 and 15-17 are physical findings of this patient (H & E, X80) (Table X)

cirrhosis may have steatorrhea, flatulent dyspepsia, impaired appetite, loss of weight, intolerance to fat, bloating, nausea and vomiting (Table III) Patients often complain of back pain and, in one instance, a patient suffered fractures of the arm and hip as a result of a mild fall

TABLE II
INCIDENCE OF INITIAL CLINICAL MANIFESTATIONS IN PRIMARY BILIARY CIRRHOSIS
(13 females, 3 males youngest age, 27, oldest age, 69, mean age, 47)

	(16 cases)	*Ahrens' (17 cases)*
Initial Manifestation	(%)	(%)
Jaundice	32	21*
Pruritus	32	55
Jaundice and pruritus	25	—
Jaundice pruritus and xanthomatosis	6	6
Xanthomatosis	6	—
Anorexia		6
Abdominal pain		6
Abdominal pain and anorexia		6
Anorexia		12
Pruritus and diarrhea		6
Diarrhea		6

*One case with melanosis

TABLE III
INCIDENCE OF EVENTUAL SYMPTOMS IN PRIMARY BILIARY CIRRHOSIS

	(16 cases)	*Ahrens (17 cases)*
Symptoms	(%)	(%)
Weakness	94	65
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due to the metabolism of tyrosine, oxidized by a catalyst, tyrosinase, to dopa and melanin, as a manifestation of inactivation of estrogen by the diseased liver and stimulation of the melanin hormone of the intermediate lobe of the pituitary gland[62,150] Lymphadenopathy particularly in the inguinal and axillary regions appeared in less than half of the cases In 3 cases of this series, abdominal exploration exposed extremely large lymph nodes in the region of the porta hepatis. Surgical biopsy of these nodes demonstrated lymphadenitis Primary biliary cirrhosis usually occurs near the anticipated time of menopause. Amenorrhea occurred in 4 cases and menorrhagia and metromenorrhagia in one each. Pregnancy did not occur in any case In Ahrens' series of 3 patients who became pregnant, only one successfully carried to term[6]

Usually within one to six years after the onset of jaundice and pruritus, slightly less than half of the patients develop cu-

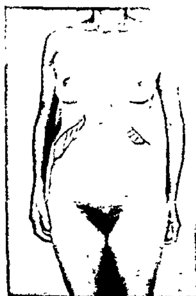


Fig 10 Hepatosplenomegaly in a female patient with primary biliary cirrhosis. Note good nutritional status

TABLE IV
INCIDENCE OF PHYSICAL FINDINGS IN PRIMARY BILIARY CIRRHOSIS

Physical Findings	*(16 cases)* (%)	*Ahrens'* (%)
Enlarged liver	94	100
Jaundice	81	94
Enlarged spleen	43	65
Cutaneous melanosis	43	65
Dry skin	43	65*
Xanthomatosis	43	48
Xanthoma planum	25	—
Xanthoma tuberosum	19	—
Papular dermatitis	31	48
Xanthelasma	25	82
Lymphadenopathy	25	48
Osteomalacia	25	48†
Ascites	12	35
Edema	12	30
Spider angioma	12	30
Palmar erythema	12	30
Loss of hair	6	—
Esophageal varices (11 cases)	45	53
Clubbed fingers	6	23

* Thick skin
†*Osteoporosis*

larged spleen, usually 2 to 6 fingerbreadths below the subcostal margin and in a jaundiced patient suggests immediately parenchymal hepatic disease Frequently, the appearance of the condition is as shown in Figure 10 with jaundice, factitial dermatitis, cutaneous melanosis, hepatosplenomegaly, kyphosis, abdominal distention, and loss of weight The other more common physical signs are lymphadenopathy, kyphosis and compression fractures of the vertebra and cutaneous findings which are observed in slightly less than half of the patients Course, dry skin, tendency to gray hair, xanthelasma, xanthomatosis and eventually stigmata of cirrhosis such as spider angioma, palmar erythema, partial loss of body hair and clubbed fingers are observed occasionally in this condition

The cutaneous pigmentation observed in biliary cirrhosis is usually darkish tan due to deposits of melanin in an icteric epidermis This is conspicuously observed in the exposed areas of the skin, nipples, and scars, and simulates the melanosis observed in hemochromatosis, adrenal insufficiency, and intestinal lipodystrophy The regulation of melanosis has been postulated to be

FIG 12a Xanthoma planum on the creases of fingers and palms. Primary biliary cirrhosis

FIG 12b Same patient twenty three months later no appreciable change

taneous xanthomata Xanthelasma, small flat fatty tumors usually on the upper eyelids, occur in many instances and their presence does not necessarily coincide with the onset of generalized xanthomatosis. One patient developed gradually a husky voice and direct laryngoscopy disclosed a laryngeal xanthomata. Two main types of xanthomata may occur in patients with primary biliary cirrhosis, namely, xanthoma planum and xanthoma tuberosum. The common areas where flat xanthomata or xanthoma planum are observed are the creases of the palms and fingers, neck, chest, site of venipuncture, and scars (Fig 10). Nodular xanthomata or xanthoma tuberosum occur less frequently These were demonstrated on the elbows, hands, fingers, wrists, scars, face and infrequently over the tendons, especially the Achilles tendon (Figs 11-14) A direct correlation usually exists between the level of cholesterol and phospholipids in the blood and the presence of xanthoma with the exception of xanthelasma [2,5,6,23,72,126,144-146] The extent of xanthomatosis subsided



Fig 11 Several small xanthoma tuberosum on the dorsum of hand near first finger of a patient with primary biliary cirrhosis



FIG. 12a Xanthoma planum on the creases of fingers and palms. Primary biliary cirrhosis



FIG. 12b Same patient twenty three months later, no appreciable change



FIG 12c Same patient Marked xanthoma tuberosum of elbows Xanthelasma were also present.

in three patients following surgical exploration of the abdomen in 1 case (Fig 13) and during the advent of hepatic insufficiency in 2 cases In each instance, the fractionated lipid values of the serum decreased Xanthomatosis, occurring in patients with primary biliary cirrhosis, has been reported to have diminished spontaneously upon the pathological development of cirrhosis and following exploratomy laporatomy.[57 127]

The clinical course of this disease is usually progressively slow and persists for one to ten years (average six years) Only in the late course of the disease, if at all, does cirrhosis manifest with hepatic insufficiency, portal hypertension and ascites (Table X) The transition from the clinical picture of obstructive jaundice to cirrhosis may be determined more reliably by serial histopathological study of hepatic biopsies and hepatic function tests than by physical findings (Table X) In contrast to portal or postnecrotic cirrhosis, histological and biochemical evidence of



FIG. 13a Extensive xanthoma tuberosum on the face of a male patient with primary biliary cirrhosis prior to an abdominal laparotomy

FIG. 13b Same patient eight months following abdominal laparotomy and surgical biopsy of an enlarged lymph node at the porta hepatis. Despite operative cholangiogram, no obstructive lesions of the extrahepatic biliary tract were found. The liver was grossly enlarged, dark green and its surface was smooth

hepatic cell necrosis occurs terminally in patients with primary biliary cirrhosis. Consequently, these patients generally are not as much of a surgical risk for portacaval shunts

LABORATORY FINDINGS

The laboratory data listed in Table V was obtained from patients with primary biliary cirrhosis generally from two to six years after the onset of their disease. As has been emphasized in several reports, this condition, particularly early in the clinical course, reflects biochemical evidence of regurgitation or obstructive jaundice: hyperbilirubinemia with elevation principally of the direct one-minute fraction, choluria, diminished fecal and variable or increased urinary urobilinogen, alkaline hyperphosphatasemia, and hypercholesterolemia.[8,112,139] Initially, hepatic

TABLE V
LABORATORY DATA IN 16 CASES OF BILIARY CIRRHOSIS

Laboratory Data	*Number of Cases*
Leucocytosis	9
Leucopenia	4
Thrombocytopenia	0
[illegible]	1
[illegible]	1
[illegible]	0
[illegible]	3
[illegible]	5
[illegible]	1
[illegible]	14
[illegible]	1 (4 cases)
[illegible]	2
[illegible]	32%
[illegible]	41
[illegible]	7.46
[illegible]	11.59

function tests indicative of hepatocellular dysfunction are normal, although it is not unusual to find the cephalin-cholesterol flocculation test positive or elevation in the thymol turbidity or zinc sulfate turbidity test, particularly if hyperlipemia exists. Recently, two women with primary biliary cirrhosis of sixteen and thirty-eight months' duration had elevated serum mucoprotein and normal values for the serum cholinesterase, serum iron and serum transaminase. It has been demonstrated that elevation of the serum mucoprotein invariably occurs in various forms of biliary obstruction, and reduction in parenchymatous or neoplastic hepatic disease.[60] As the condition progresses the hepatic flocculation tests become abnormal, the serum cholinesterase decreases and transaminase increases. However, these newer hepatic function tests do not provide any clue which will assist in the differentiation of primary and secondary biliary cirrhosis or cholestatic disease.[70] A radioactive (I^{131}-tagged) rose-bengal uptake excretion test has been employed with initial success in patients with primary biliary obstruction.[136] Electrophoretic patterns of serum protein or fractional biochemical determinations of the serum protein in these patients may be normal, or may demonstrate low albumin, high fraction values of the beta-globulin fraction and eventually increased gamma globulin (Chapter





FIG 13c and d Same patient before, and eight months postoperatively, extensive bizarre appearance of xanthoma tuberosum of both aspects of hands and distal forearm, with facial xanthomata before and eight months postoperatively Note marked resolution of xanthomata following abdominal laparotomy (Courtesy, Spellberg and Ghattas—Gastroenterology—Feb, 1955)

TABLE V
LABORATORY DATA IN 16 CASES OF BILIARY CIRRHOSIS

Laboratory Data	Number of Cases
Leucocytosis	9
Leucopenia	4
Thrombocytopenia	0
Normochromic, normocytic anemia	1
Hypoalbuminemia	1
Hyperglobulinemia	0
Abnormal cephalin cholesterol floc[illegible]	3
[illegible]	5
[illegible]	1
[illegible]	14
[illegible]	1 (4 cases)
[illegible]	2
[illegible]	32%
[illegible]	44
[illegible]	7 46
	11.59

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The malabsorption syndrome (hepatobiliary steatorrhea) has been noted in patients with chronic biliary obstruction.[11] Various special diagnostic studies have been used in patients with primary biliary cirrhosis. In two instances, the pancreatic secretin test was performed because of the established steatorrhea and the presence of a deficiency (sprue) pattern in the roentgenograms of the small intestine (Fig. 15). Ten of fifteen patients in Ahrens series had deficiency patterns in the small intestine.[5] The result of these tests disclosed normal values for volume of pancreatic juice, pH, bicarbonate, chloride, trypsin, amylase and lipase. Stool examinations from the same cases disclosed no neutral fat and muscle fibers. One patient was placed on the Mayo Clinic steatorrhea test diet for quantitative determination of steatorrhea and azotorrhea. This diet consists of 2,460 calories, 102 gm. of fat, 118 gm. of protein, and 270 gm. of carbohydrate and was continued for five days. The stool collected marked by carmine for a period of seventy two consecutive hours. The fecal fat was found to be 7.1 gm. per twenty four hours (range 1.8 to 6.7 gm.) and fecal nitrogen 2.3 gm. (range 0.8 to 2.5 gm.). The oral administration of bile salts to this patient resulted in subjective clinical improvement in the steatorrhea and fat intolerance. In the same patient, the oral vitamin and tolerance test curve was low but not flat. A tolerance test using I^{131} Triolein has been employed to study the malabsorption syndrome. Serial determinations of the lipid I^{131} level in the blood were flat in sprue and low in patients with either obstructive jaundice or chronic pancreatitis.[12]

It has been demonstrated that the levels of serum cholesterol and phospholipids are elevated in patients with primary biliary cirrhosis and that the presence of xanthomatosis depends upon the height of these levels (Table VI). Unlike other types of xanthomatosis, the sera of patients with biliary cirrhosis is clear rather than milky. Regression of xanthomatosis, on the other hand, correlates with a decrease of these abnormally elevated lipid levels, and may occur spontaneously or as a manifestation of progressive hepatic insufficiency. Xanthomatosis and hyperlipemia occur in several other diseases but, in contrast to primary biliary cirrhosis,

16, Fig. 2).[6,79,112,126,127,132] Plasma lipoproteins have been studied in primary biliary cirrhosis. Most of the lipids in this condition are combined atypically with three beta globulins as low density lipoproteins within the S_f 10-20 classes.[120] Generally, while little diagnostic significance has been attached to the quantitative determination of fractional serum proteins in cirrhosis, it has been noted that the biliary variety commonly has elevated beta fraction, and, as the cirrhosis becomes advanced, the gamma fraction predominates quantitatively. A high titer of autoantibody has been reported in this condition.[58] A normochromic, normocytic anemia may also be observed. In the current series leukocytosis was observed in over half of the cases. In Ahrens' series, an eosinophilia was present in 9 of 17 cases.[6] No clinical or hematologic evidence of hypersplenism was noted in any of the cases of primary biliary cirrhosis.[6] He also found elevated BMR's in 11 of 13 patients with primary biliary cirrhosis in whom there was no clinical evidence of thyroid dysfunction.

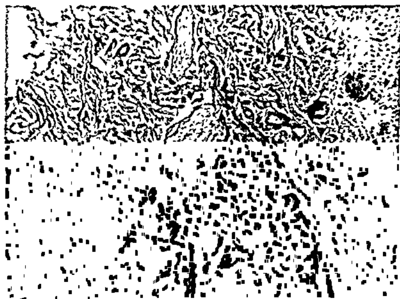


Fig. 14. Histological specimen of a xanthoma tuberosum obtained from a patient with primary biliary cirrhosis, compact foam cells and fibrous connective tissue (H & E, X80)

TABLE VI
BIOCHEMICAL RESULTS OF FRACTIONAL PLASMA LIPIDS
IN
PRIMARY BILIARY CIRRHOSIS
(8 Cases)

	Without Xanthomatosis (mg./100 cc.) 4 Cases	With Xanthomatosis (mg./100 cc.) 4 Cases
Cholesterol (Normal 150-250 mg./100 cc.)		
Lowest	301	536
Highest	815	1,398
Mean	526	1,026
Cholesterol esters (Normal 60-75% of cholesterol)		
Lowest	115	127
Highest	350	616
Mean	216	375
Free fatty acids (Normal 250-390 mg./100 cc.)		
Lowest	110	155
Highest	327	526
Mean	204	389
Neutral fat (Normal 25-600 mg./100 cc.)		
Lowest	164	155
Highest	487	502
Mean	230	327
Phospholipids as lecithin (Normal 110-250 mg./100 cc.)		
Lowest	295	557
Highest	2,225	2,852
Mean	742	1,520
Total lipids (Normal 450-1,100 mg./100 cc.)		
Lowest	814	1,424
Highest	3,610	5,126
Mean	2,204	3,452

are usually not characterized by clear serum and markedly elevated serum phospholipids. Among these conditions are, diabetes mellitus, chronic relapsing pancreatitis, familial and idiopathic hyperlipemia, von Gierke's disease, and nephrosis (Table VIII). On the other hand, familial hypercholesterolemia and hypercholesterolemia associated with hypothyroidism and icterogenic drugs are conditions in which the serum is clear (Table IX). In hyperlipemia from estrogenic therapy, the serum is milky. Xanthomatosis and normocholesterolemia are observed in patients with Hand-Schuller-Christian syndrome.[2,8,38,39,124,137] However, in one of our patients, a fifty-two year old woman, the serum was turbid, but in the remaining cases was translucent. The neutral fat in the former case was 502 mg./100 cc. of blood (normal 25 to 600 mg./100 cc. of blood). Markedly elevated phospholipid values are characteristic of any type of biliary obstruction whether intra



Fig 15 Primary biliary cirrhosis Quantitatively biochemically established hepatobiliary steatorrhea, roentgenogram of the small intestine taken four hours following ingestion of barium, moulage pattern, segmentation, hypomotility, distended loops, and feathery pattern

of Ahrens an entirely different mechanism exists in the deposition of lipids in the skin and in the arterial intima.[2] Ahrens and Kunkel have shown that patients with elevation of total serum lipid usually above 2,000 mg./100 cc. had cutaneous xanthomatosis (Table VII). Ahrens and Kunkel have demonstrated that clarity of high lipid sera is closely correlated with elevated proportions of serum phospholipids, and lipemia (milkiness) with low proportions of phospholipids.[2,4,5] The present fractionated series serum lipid values, on the other hand, shows some overlapping. Xanthomatosis occurred in one patient when the total serum lipid was 1,424 mg./100 cc. and absent in another case when the level was 3,610 mg./100 cc. Generally, a fairly typical lipid pattern is present in this condition and the degree varies proportionately with the presence of xanthomatosis.

TABLE IX
BIOCHEMICAL STUDIES IN CHLORPROMAZINE (THORAZINE) HEPATITIS

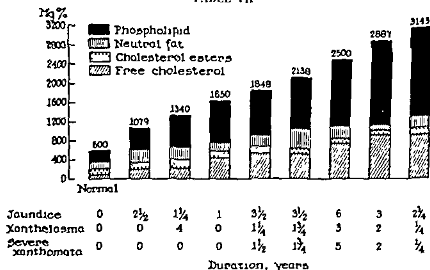
[illegible]

	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	8.7		
[illegible]	2.4	2.5	[illegible]		1.9	
[illegible]	0			0	0	[illegible]
[illegible]	[illegible]			320	300	270
[illegible]	[illegible]	[illegible]		[illegible]		
[illegible]				[illegible]		
[illegible]	10%				[illegible]	
BSP/45 [illegible]					21%	6%

Skeletal pain, principally thoracolumbar backache is a frequent complaint of patients with primary biliary cirrhosis and is usually due to osteomalacia or and osteoporosis.[8,17,71,114] This is observed radiologically by fractures of the vertebra (Fig. 16), kyphosis, and decalcification of the bone. Impaired intestinal absorption of fat as the result of biliary obstruction, avitaminosis D, impaired absorption of calcium, and the malabsorption syndrome with hypocalcemia, hypophosphorusemia and negative nitrogen balance contribute to the formation of these osseous

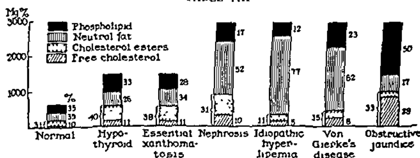
hepatic or extrahepatic in origin, or the consequence of the administration of icterogenic drugs. Along this line, it has been noted that methyl testosterone administered orally to these patients as an antipruritic agent produces a decrease in all of the lipid fractions and increased hyperbilirubinemia. Arterial atherosclerosis was minimally developed in the three necropsy cases, and in the opinion

TABLE VII



SERUM LIPID PATTERNS IN EIGHT PATIENTS WITH PRIMARY BILIARY CIRRHOSIS
(Ahrens and Kunkel, J Clin Investigation 1950)

TABLE VIII



REPRESENTATIVE LIPID PATTERNS IN VARIOUS HYPERLIPEMIC CONDITIONS
(Ahrens and Kunkel, J Clin Investigation, 1950)



FIG 16 Roentgenogram of the thoracic vertebrae of a patient with primary biliary cirrhosis who complained of moderate back pain Kyphosis, osteomalacia (and osteoporosis) and eventual collapse of T_{10} vertabra

Clinical and Laboratory Data of a 47-Year Old Woman with Primary Biliary Cirrhosis and Xanthomatosis
(Death occurred during thirty fourth month from hemorrhagic esophageal varices)

Clinical Manifestations		Months 0	1 mo	6 mo	12 mo	21 mo	27 mo
Jaundice		+	+	+	+	+	+
Dark urine		+	+	+	+	+	+
Pruritus		+	+	+	+	+	0
Melanosis		—	+	+	+	+	+
Body weight, lbs		—	109	108	112	117	120
Bone pain		0	+	+	+	+	0
Steatorrhea		+	+	+	+	+	+
Xanthoma planum		0	0	+	+	+	+
Xanthoma tuberosum		0	0	0	+	+	+
Xanthelasma		+	+	+	+	+	+
Lymphadenopathy		+	+	+	+	+	+
Hepatomegaly		0	1f	4f	5f	5f	5f
Splenomegaly		0	0	2f	3f	1f	1f
Dry skin		0	0	+	+	+	+
Nocturnal diuresis		0	+	+	+	0	0
Laboratory Data	*Normal*						
Serum bilirubin, mg /100 cc D/T	0.2 / 1.0	—	4.6 / 7.9	6.7 / 10.2	7.5 / 11.6	1.2 / 8.6	2.1+ / 5.3
Blood alk. phosphatase, Bodansky units	2.5-5.0	—	18.7	20	19	21	17
Blood cholesterol, mg /100 cc	30- 250	—	5.9	727	701	609	290
Blood cholesterol esters mg /100 cc	50-65%	—	287	329	—	312	220
Blood phospholipids, mg /100 cc	110- 250	—	1,520	1,560	—	984	301
*Blood total lipids, mg /100 cc	450-1,100	—	2,825	2,926	—	1,850	850
Serum albumin, gm /100 cc.	4.5-5.5	—	2.4	4.9	3.6	3.3	3.6
Serum globulin, gm /100 cc.	1.5-3.0	—	3.4	2.6	3.6	3.8	4.1
Cephalin cholesterol flocculation, 48 hours	2	—	0	2+	2+	2+	3+
Thymol turbidity, units	0-7	—	—	9.8	9.5	11.7	13.0
Zinc sulfate turbidity test, units	3.5-10	—	—	16.2	15.4	13.2	15.2
Prothrombin time, per cent	100%	—	30	67	36	49	36
Serum neutral fats, per 100 cc	25- 600		102				
Operation	Cholecystojejunostomy						
Treatment	40 m fat, high protein, high caloric diet and oral bile salts						

*Serum clear, †Elevated serum iron, 280 mg per 100 cc, serum mucoprotein, 13.5 mg % per 100 cc; serum cholinesterase 0.44ΔpH, and serum transaminase (SGO-T) 361 micromols/100 cc.



FIG. 17 Operative cholangiogram from a patient with primary biliary cirrhosis (Table X Fig. 4). This procedure demonstrated patency of the intrahepatic and extrahepatic biliary ducts necessary to confirm unequivocally a clinical diagnosis of primary biliary cirrhosis

conditions. Ahrens has noted marked dental caries and loose teeth in over half of his series.[6]

It has been established that, at the present time, the only reliable differential diagnostic criterion to distinguish primary from secondary biliary cirrhosis or cholestatic disease is the determination of patency of the extrahepatic biliary system. This may be accomplished by operative cholangiogram which is reported to have been performed under local anesthesia by direct cholecysto-cholangiography or by abdominal laporatomy (Fig. 17)[130] Operative cholangiograms through a T-tube were mandatory in confirming the diagnosis in 7 patients. Exploratory laporatomy was employed to confirm the absence of extrahepatic biliary obstruction in the remaining cases. In 5 more patients suspected of having "primary biliary cirrhosis" operative exploration of the biliary region revealed 3 patients with pancreatic adenocarcinoma and 2 patients with choledocholithiasis. Intravenous or oral cholangiography are unreliable diagnostic procedures to demonstrate patency of extrahepatic biliary system, because, as one would expect, excretory function of the liver is markedly impaired in primary biliary cirrhosis[13,24,96,99]

IMMEDIATE AND CONTRIBUTORY CAUSES OF DEATH

The cause of death in 3 patients was hepatic insufficiency. Portal hypertension developed in 1 case, but rupture of the esophageal varices did not occur. Eight of Ahrens' 17 cases demonstrated esophageal varices, resulting in bleeding in 4 cases, one of which died as the result[6] Hepatic insufficiency was the cause of death in 4 of his series Hepatic failure, esophageal hemorrhage, bronchopneumonia are the most commonly reported causes of death in this condition.

TREATMENT

The therapeutic management of patients with established primary biliary cirrhosis consists of relief of the symptoms of biliary obstruction together with the conventional management of cirrhosis (Chapter 16) Ahrens and Spellberg have reported respectively the occurrence of markedly enlarged lymph nodes,

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3 ——— Harris R. C., and MacMahon, H. E., Atresia of the Intrahepatic Bile Ducts, Pediatrics, 8 628 1951

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7 Allen J. E. and Reynolds J. M. Intrahepatic Obstructive Jaundice During Prolonged Administration of Propylthiouracil South M J 49 608 1956

8 Aschoff, L. Die Erkrankungen der steinfreien Gallenwege Anatomisches Referat Ver handl deutsch Gesellsch inn Med 44 261 1932

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12 Berg P., Wenger, J. and Kirsner J. B. The Use of I[131] Triolein in the Study of Absorptive Disorders in Man Gastroenterology 32 1 1957

13 Berk, J. E. Stauffer H. M. Shay H., and Karnofsky, R. E. The Normal and Abnormal Biliary Tract as Shown by I. V. Cholecystography and Cholangiography Gastroenterology 28 230, 1955

14 Best, M. H. Duncan C. H. Van Loon, E. J. and Wathen J. D. The Effects of Sitosterol on Serum Lipids Am J Med 19 61 1955

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16 Brown N. L. and Shnitka, T. K. Constitutional Non hemolytic Jaundice with Lipochrome Hepatosis (Dubin Sprinz Disease) Am J Med 21 292 1956

17 Buchbinder, W. C. and Kern R. Blood Calcium Deficiency in Experimental Obstructive Jaundice, Am J Physiol 80 273 1927

18 Bürger, M. and Grütz O. Über hepatosplenomegale Lipoidose mit xanthomatösen Veränderungen in Haut und Schleimhaut Arch Dermat u Syph, 166 542 1932

19 Cannemeyer, W., Thompson, J. R. and Lichtenstein, M. R., Severe Para aminosalicylic Acid Hypersensitivity Blood and Lymph Node Studies Blood, 10 62, 1955

20 Cantarow, A., and Bucher C. W. Hemochromatosis Report of a Case Arch Int Med 67 333, 1941

particularly in the region of the porta hepatis, in primary biliary cirrhosis which may perpetuate obstructive jaundice and xanthomatosis.[6,127] Surgical diagnostic confirmation of primary biliary cirrhosis by laparotomy may also effect a spontaneous remission as reported by Spellberg and Gattas.[127] On the other hand, T-tube drainage of the common bile duct or a cholecystojejunostomy performed in patients with primary biliary cirrhosis to alleviate pruritus and jaundice may be satisfactory. Multiple needle biopsies of the liver rather than an isolated wedge biopsy are recommended during the operative procedure. The oral administration of bile salts in doses of 1.0 to 2.0 gm. after meals and a low-fat, high-protein, high caloric diet may control fat intolerance and steatorrhea. It has been demonstrated that quantitatively reduced steatorrhea follows oral administration of bile salts.[41,45,71] Frequently, patients may derive comfort from a 40 gm. fat diet despite its assumed unpalatableness and its failure to reduce hypercholesterolemia[67] (Chapter 17). It has been noted that the intestinal absorption of exogenous cholesterol is impaired in complete biliary obstruction and, therefore, reduction of hypercholesterolemia may not be predicted when this diet is prescribed.[120] Because of steatorrhea, the administration of supplements of the fat-soluble vitamins, particularly A, D, and K is recommended in this condition.

Osteoporosis and osteomalacia are treated by a high-protein diet, vitamin D, bile salts, orthopedic braces and appliances, and limitation of weight bearing. Calcium gluconate or lactate orally generally in a dose of one gram per day, is recommended. The management of intractable pruritus, the major therapeutic obstacle in cases of primary biliary cirrhosis, is discussed in Chapter 16. Corticosteroid therapy has been found therapeutically valueless in this condition.[21] The use of lecithin or sitosterol has been demonstrated to reduce hypercholesterolemia.[63,90] Whether this is beneficial in primary biliary cirrhosis with xanthomatosis, although presumably dubious, remains to be confirmed.

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Chapter 9

SECONDARY BILIARY CIRRHOSIS

SECONDARY BILIARY cirrhosis occurs infrequently as the result of chronic obstructive lesions of the extrahepatic biliary system. This condition usually follows intermittent or prolonged episodes of obstructive jaundice. When biliary cirrhosis eventually develops, hepatic insufficiency, portal hypertension, ascites, chronic obstructive jaundice, cutaneous melanosis, pruritus and marked hepatosplenomegaly are the salient clinical findings. Pathologically, the liver grossly resembles portal cirrhosis in addition to stasis of bile. The validity of several reports of secondary biliary cirrhosis is dubious when the morphological criteria of cirrhosis are absent, particularly nodular regeneration, or other recognized pathogenetic factors of cirrhosis, such as malnutrition or viral hepatitis are suspected of playing a unique etiological role. It has been recognized that biliary obstruction inhibits hepatic regeneration, and for this reason, cirrhosis would appear to occur rarely.[29,37,48,54]

According to Gibson and Robertson, Jones first reported biliary cirrhosis in the *Transactions of the Pathologic Society of London* in 1851.[30] Wickham Legg in 1873 adequately described secondary biliary cirrhosis pathologically.[45,73] Meyer in 1872 and Charcot and Gombault in 1876 experimentally ligated the common bile duct and noted dilatation of the intrahepatic biliary ducts and hepatic fibrosis.[13,45] They believed that these morphological changes were due to the irritating property of bile. Thereafter there was much controversy whether or not biliary obstruction actually could produce cirrhosis.[29,62-64,73] Mangelsdorf reported that up to 1882, there were 181 authentic published reports of cirrhosis as the result of biliary obstruction. Ford in 1901 reported 21 more cases.[27] Mallory in 1911 considered three pathological conditions of the liver, namely, fatty infiltration, chronic passive congestion, and biliary obstruction, capable of producing cirrhosis.[52] Infectious, obstructive, or biliary cirrhosis were often

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FIG 2 Sagittal section of liver with fascioliasis Flukes produce dilation, thickening and tortuosity lodged in the biliary ducts and chronic biliary obstruction (Courtesy, Ash and Spitz—Pathology of Tropical Diseases—W B Saunders Co and Armed Forces Institute of Pathology)

langiolitic biliary cirrhosis due to "toxic alterations" in the small intrahepatic bile ducts [51]

The experimental production of secondary biliary cirrhosis was demonstrated originally by Richardson in 1911 and subsequently confirmed by others [7,49,50,51,73,82] These studies disclosed that ligation of the common bile duct produced distention and tortuosity of the intrahepatic bile ducts, focal parenchymal degeneration, stasis of bile in the hepatic lobules dilatation and fibrosis of the larger intrahepatic blood vessels and proliferation of the portal connective tissue Eventually, nodular regeneration of the liver may occur, but this histopathological finding has not been consistently produced by experimental ligation of the common bile ducts That cirrhosis produced exclusively by mechanical obstruction of the extra-hepatic bile ducts has been questioned,

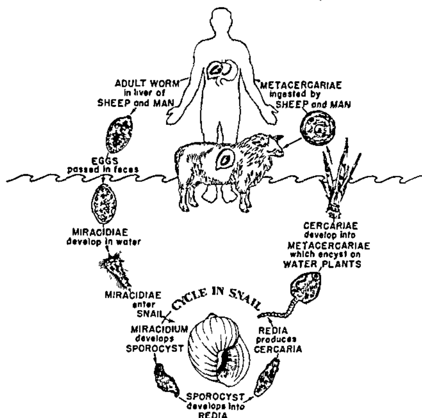


FIG 1 Descriptive life cycle of the sheep liver fluke, Fasciola hepatica (Courtesy, Ash and Spitz—Pathology of Tropical Diseases—W B Saunders Co, and Armed Forces Institute of Pathology)

employed synonymously to explain cirrhosis caused by infection in bile ducts as the result of biliary stasis This type of cirrhosis has been called Charcot's biliary cirrhosis[12] Rossle eventually classified three distinct types of biliary cirrhosis: cholestatic biliary cirrhosis due to chronic extrahepatic biliary obstruction; cholangitic biliary cirrhosis due to mechanical blockage of the extrahepatic biliary system associated with cholangitis, and cho-

2 cases, and carcinoma of the gallbladder and metastatic carcinoma in 1 each.[20] It is generally not appreciated that neoplastic obstructive lesions of the extrahepatic biliary tract may produce biliary cirrhosis.[43] In these instances, chronic obstructive jaundice persists for at least twelve to eighteen months. Schmitz and Sinaiko reported that neoplastic biliary lesions occurred in secondary biliary cirrhosis in over half of 93 cases.[73a]

Shay and Harris reviewed the literature and reported a case

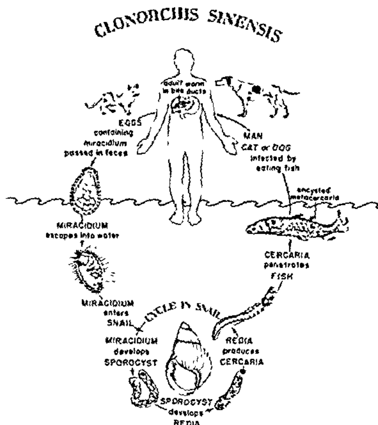


FIG. 3. Descriptive life cycle of the Chinese liver fluke, Clonorchis sinensis. (Courtesy Ash and Spitz—Pathology of Tropical Diseases—W. B. Saunders Co., and Armed Forces Institute of Pathology.)

is noted by the fact that "toxins," infection, malnutrition, infarction and the necrotic property of bile have been considered as additional pathogenetic factors.[21,71,74,77] Generally, there are no uniform pathological effects of biliary obstruction either in the experimental or human livers.

TABLE I
Etiological Factors in 12 Cases of Secondary Biliary Cirrhosis
(12 Cases)

	Cases
Postoperative stricture common bile duct	8
Common duct stone	1
Carcinoma of pancreas	1
Fasciola hepatica infestation	1
Carcinoma of ampulla of vater	1

ETIOLOGY

The most common obstructive lesions in patients with secondary biliary cirrhosis are postoperative stricture of the common bile duct and choledocholithiasis (Table I). Gibson and Robertson in a careful study of 244 necropsies of chronic biliary obstruction and obstructive jaundice found that the incidence of secondary biliary cirrhosis was 8.6 per cent.[30] Postoperative stricture of the common bile duct was present in 10 cases, choledocholithiasis in 6 cases, ampullary carcinoma in 2 cases, and carcinoma at the head of the pancreas, infiltrating carcinoma of the gallbladder, and carcinoma of the stomach each in 1 case, respectively. Leevy and his associates found that the incidence of biliary cirrhosis among 34 cases of obstructive jaundice was 12 per cent, and postulated that persistent biliary obstruction and cholangitis together produced cirrhosis.[44] Stenosis of the sphincter of Oddi has been recognized recently and may produce secondary biliary cirrhosis.[9] Secondary biliary cirrhosis was a complication of 26 per cent of operative bile-duct injuries in one series.[60]

The nature of the obstructive lesion in 51 patients with secondary biliary cirrhosis reported by Doehlert and his associates was stricture of the common bile duct in 25 cases, stricture of the hepatic duct in 5 cases, choledocholithiasis in 14 cases, carcinoma of the pancreas in 6 cases, carcinoma of the common bile duct in

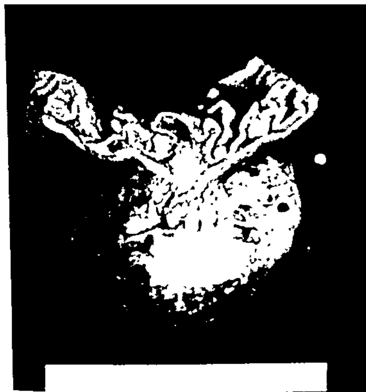


FIG 5 Surgical specimen of an adenocarcinoma of pancreas resected during a pancreaticoduodenectomy, neoplastic obstructive jaundice had been present for one year, asymptomatic secondary biliary cirrhosis was discovered at the time of the surgical operation

(Figs 3, 4). Hoeppli studied the livers of 66 Chinese with clonorchiasis and found two cases of cirrhosis, one of which was portal and the other due to the liver fluke [31] As a result of infestation by these two types of liver flukes, the hepatic and common bile ducts become chronically inflamed and thickened Proliferation of fibrous connective tissue in the portal space, cellular infiltration, and, occasionally, proliferation of the bile ducts occur in the liver, Eventually there is progressive parenchymal



Fig 4 Sagittal section of a liver with Clonorchiasis Flukes infest and produce dilated, thickened intrahepatic bile ducts (Courtesy, Ash and Spitz—Pathology of Tropical Diseases—W B Saunders Co, and Armed Forces Institute of Pathology)

of biliary cirrhosis with cutaneous xanthomatosis and also xanthomata occurring within the larger bile ducts inside and outside the liver[73 84,88] This clinical and laboratory picture of this type of secondary biliary cirrhosis was indistinguishable from primary biliary cirrhosis with xanthomatosis Malformation and partial or complete atresia of the common bile duct are the most common types of extrahepatic biliary obstructions in infants and children producing secondary biliary cirrhosis (Chapter 12)

Secondary biliary cirrhosis may occur as the result of parasitic infestation in the common and hepatic bile ducts This has been named zooparasitic cirrhosis and is found more in the tropical areas of the world Recently a clinical study was reported of a merchant seaman who had complained of episodic biliary colic, jaundice, fever, and chills of several years' duration[41a] Surgical exploration of the common bile duct revealed six well-developed Fasciola hepatica flukes Histological examination of a biopsy of the common bile duct disclosed ova (Figs. 1, 2) Another liver fluke which produces biliary cirrhosis is the Clonorchis sinensis (Chinese liver fluke) which is prevalent in the Orient.[35 38,39 91]

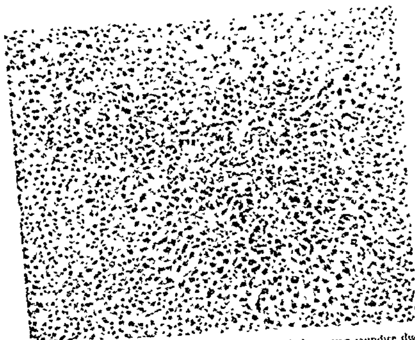


FIG. 82. Histological picture of a liver from a case of obstructive jaundice due to inoperable and fatal carcinoma of pancreas. Note particularly marked stasis of bile, distention of biliary canaliculi, 'bile thrombi' and minimal hepatocellular necrosis (H. & E. ×100)

damage with the formation of cirrhosis. Ascaris lumbricoides is also known to infest the biliary tract and produce obstructive jaundice. Biliary cirrhosis due to this roundworm, however, is apparently rare. Schistosomiasis has been implicated in the pathogenesis of cirrhosis. These parasites lodge in the portal veins of the liver and produce a 'pipestem cirrhosis' or portal vein fibrosis rather than a true cirrhosis.[illegible] Hepatosplenomegaly, esophageal varices, and ascites, however, occur as a result of the extensive hepatic fibrosis.[39] That schistosomiasis produces cirrhosis has been upheld in several reports and denied by others.[35, illegible] It has been suggested that malnutrition plays a greater role than parasitic infestation in 'zooparasitic cirrhosis'.[29, 57, 82]



Fig 6 Gross liver representing secondary biliary cirrhosis Finely granular, greenish colored cirrhosis, weight 1,920 gm, choledocholithiasis was the principal finding at necropsy to account for chronic obstruction of the biliary tract

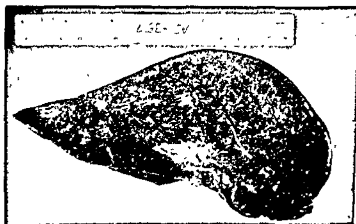


Fig. 7 Sagittal section of an enlarged liver with marked cholestasis Cirrhosis had not developed, obstructive jaundice had occurred for seven months, postoperatively an inoperable and metastatic adenocarcinoma ampulla of Vater was discovered Death was due to carcinomatosis

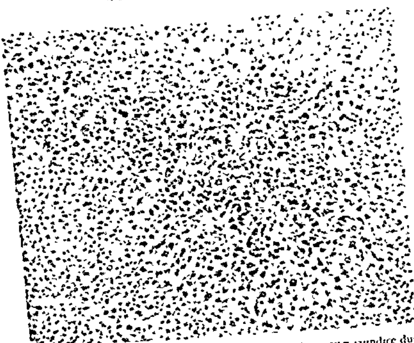


Fig. 82. Histological picture of a liver from a case of obstructive jaundice due to inoperable and fatal carcinoma of pancreas. Note particularly marked stasis of bile, distention of biliary canaliculi, 'bile thrombi' and minimal hepatocellular necrosis (H & E, X100)

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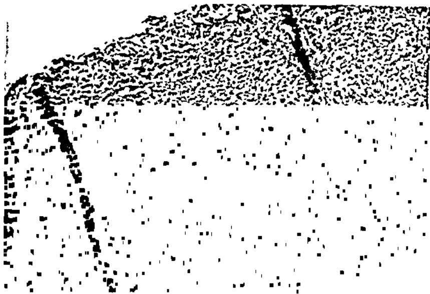


Fig 8b Needle biopsy of the liver from a case of early secondary biliary cirrhosis due to recently symptomatic choledocholithiasis in a twenty-one year old male Jaundice was present eight months before choledocholithotomy Note histological findings as stasis of bile, dilatation of biliary canaliculi, proliferation of stoma, hepatocellular degeneration and the early formation of nodular regeneration (H & E, X80)

PATHOLOGICAL FEATURES

Gibson and Robertson in 1939 emphasized strict gross morphological features in 13 cases of secondary biliary cirrhosis, among which were nodular regeneration [30] So unique was their pathological description of biliary cirrhosis in contrast to previous reports of this condition in the literature that they labeled their cases as "cirrhosis from biliary obstruction" More recently, Doehlert and his associates compared the clinical and pathological features of 27 cases each of early and advanced obstructive biliary cirrhosis with 27 cases of (alcoholic) portal cirrhosis [20] They based their pathological criteria of any type of cirrhosis, namely, hepatocellular degeneration or necrosis, nodular regeneration with distortion of the normal lobular architecture and circulatory relationships, and an increase of fibrous tissue

Table II lists the important pathological findings in 5 cases of secondary biliary cirrhosis (Figs. 5, 6). Doehlert reported the average weight of the livers in early biliary cirrhosis was 1,839 gm., in advanced biliary cirrhosis, 1,937 gm., and in portal cirrhosis, 1,958 gm. This study also revealed that the average weight of the spleens in early biliary cirrhosis was 258 gm., in advanced biliary cirrhosis, 506 gm., and in portal cirrhosis, 461 gm. Esophageal varices were demonstrated in 9 of 27 cases of advanced biliary cirrhosis, in 1 of 27 of early biliary cirrhosis, and 21 of 27 cases of portal cirrhosis. Ascites over 500 cc. was present in 14 cases of advanced biliary cirrhosis, in 11 cases of early biliary cirrhosis, and in 23 cases of portal cirrhosis.

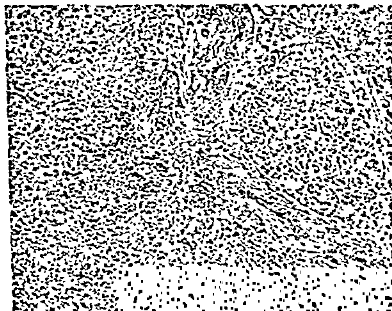


FIG. 9a. Section of liver from a case of secondary biliary cirrhosis due to common duct stone producing for at least five years biliary colic and Charcot's intermittent fever. Nodular regeneration, fibrosis, hepatocellular degeneration, dilated biliary canaliculi and bile stasis in regenerative nodules and stroma, in addition, there is marked chronic pericholangitis and perilobular parenchymal necrosis (H & E, X150)

TABLE II
PERTINENT NECROPSY DATA IN FIVE CASES OF SECONDARY BILIARY CIRRHOSIS

Weight of liver	
Largest,	2 801 gm.
Smallest	1,250 gm
Mean Weight	1,731 gm
Weight of spleen	
Largest,	530 gm
Smallest,	287 gm.
Mean Weight	312 gm
Esophageal varices	2 cases
Ascites	4 cases
Edema	4 cases
Hydrothorax	3 cases
Peritonitis	1 case
Hydrohepatosis	2 cases

There are two additional gross pathological features found in secondary biliary cirrhosis One is hydrohepatosis, present in 2 of 5 livers with secondary biliary cirrhosis. In 1926, Counseller and McIndoe employed this term primarily to describe atrophy of the hepatic parenchyma due to increased intrahepatic pressure of thickened, dilated bile ducts [17] The other morphological feature of the liver of secondary biliary cirrhosis is green or greenish-brown pigmentation (Fig 7). It has been suggested that nodular regeneration in secondary biliary cirrhosis simulates that observed in portal cirrhosis, but is less well developed and not as distinctive [20]

Histological examination of the liver of secondary biliary cirrhosis discloses marked dilatation and stasis of bile in the biliary canaliculi and bile ducts, bile-pigmentation, regeneration, degeneration and necrosis of hepatic cells, inflammatory exudate and proliferation of bile ducts in the portal area, parenchymal infiltration with polymorphonuclear leukocytes and lymphocytes, increased fibrous connective tissue, and nodular regeneration (Figs 8, 9) "Bile lakes" or "bile thrombi" located in the hepatic parenchyma may also be observed in secondary biliary cirrhosis [41,70 90] Popper and Szanto have called attention to the difficulty in histological diagnosis of various types of hepatic diseases associated with biliary obstruction, whether it is intrahepatic or extrahepatic.[63] The regenerative nodules observed in secondary biliary cirrhosis are smaller than those present in the



FIG 9b Same specimen at higher magnification showing the perilobular and stromal lesions (H & E, X300)

portal type and do not distort and compress the hepatic venules Intrahepatic stasis of bile, proliferation of bile ducts, and relative absence of alcoholic hyaline bodies are found more commonly in biliary than portal cirrhosis Serial histopathological studies of the liver have disclosed the transition from cholestatic hepatic disease to biliary cirrhosis [35 59]

Some observers have felt that biliary tract infection or cholangitis plays an important pathogenetic role in secondary biliary cirrhosis In this instance, the term cholangitic obstructive biliary cirrhosis is employed instead of cholestatic biliary cirrhosis, due to the absence of hepatic abscesses and more pronounced inflammation in the biliary ducts [35 71 72] However, the significance of distinguishing these types is controversial Moschcowitz has studied the morphology of biliary cirrhosis and postulates that angiogenesis and proliferation of bile ductules occur as compensatory

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Hydrothorax	3 cases
Peritonitis	1 case
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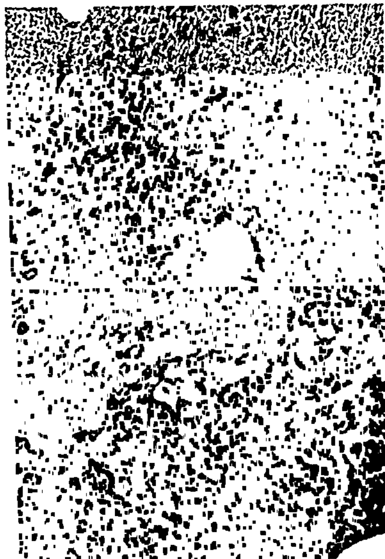


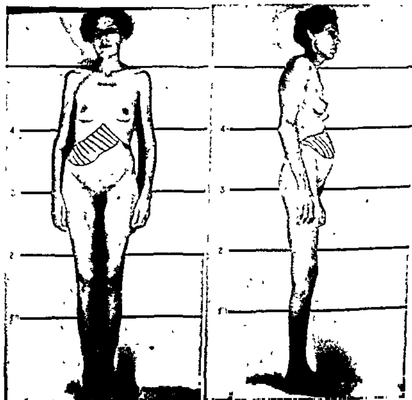
Fig. 10c. Needle biopsy of liver from same patient during the same period of clinical observation: dilated biliary canaliculi and minimal chronic pericholangitis (H & E, X150)

Fig. 10d. Same patient. Surgical biopsy of the liver obtained twelve months later. Secondary biliary cirrhosis. Note in particular regenerative nodule and marked fibrous stroma have developed histologically. (H & E, X300)

measures to restore the circulation of blood and bile.[58] Himsworth uses the term chronic cholangio-hepatitis in lieu of biliary cirrhosis He states that the degree and speed of development of this lesion is dependent upon the severity and chronicity of inflammation of the bile ducts.[31]

CLINICAL FEATURES

It has been stated that secondary biliary cirrhosis occurs only following prolonged biliary obstruction.[20 30,62 63,77,89 90] The average duration of obstructive jaundice in Doehlert's series of early



Fi ... with obstructive jaundice for less than a year (Table IX) Hepatosplenomegaly, laporatomy scar, intense jaundice, factitious pruritus and melanosis, hepato biliary steatorrhea, malnutrition, thoracic kyphosis, furunculosis, abdominal *distention;* patient procrastinated for more than twelve months before submitting to a biliary tract surgical operation Adenocarcinoma of the Pancreas, metastatic.

cept for intermittent obstructive jaundice, the symptoms of secondary biliary cirrhosis are not diagnostic. The presence of a healed abdominal surgical scar, obstructive jaundice, abdominal pain, fever, and chills is observed in both types of biliary cirrhosis. One case of secondary biliary cirrhosis had had typical Charcot's intermittent fever. On the other hand, painless jaundice was present in 5 cases.

TABLE IV
INCIDENCE OF EVENTUAL SYMPTOMS IN SECONDARY BILIARY CIRRHOSIS
(12 Cases)

	Cases
Jaundice	12
Weakness	11
Weight loss	10
Pruritus	8
Fever	7
Abdominal pain	7
Anorexia	3
Steatorrhea	3
Bleeding tendency	2
Gastrointestinal hemorrhage	1
Ascites and edema	1

TABLE V
INCIDENCE OF PHYSICAL FINDINGS IN SECONDARY BILIARY CIRRHOSIS
(12 Cases)

	Cases
Jaundice	12
Enlarged liver	12
Weight loss	11
Abdominal post operative scars	11
Enlarged spleen	8
Dry skin	6
Edema	6
Spider angioma	5
Palmar erythema	4
Esophageal varices	4 (10) *
Ascites	3
Cutaneous melanosis	3
Alopecia	1
Xanthoma planum	1

*Number of cases studied.

The physical findings of secondary biliary cirrhosis are listed in Table V (Fig 10) These findings also do not differ essentially from those demonstrated in primary biliary cirrhosis In Doehlert's series of 27 cases each of early and advanced biliary cirrhosis, ascites was present in 4 and 10 cases, respectively, eso-

biliary cirrhosis was 2 9 years and in advanced biliary cirrhosis 4 9 years[29] In *Gibson and Robertson's study, it was 3.0 years, 6* months in cases of neoplastic obstruction and 3.8 years in benign obstruction of the common bile duct.[30] The duration of life after jaundice in the series is similar. The average duration of life in the current series of cases of benign obstructive jaundice was 3 2 years One patient with secondary biliary cirrhosis was jaundiced due to choledocholithiasis for a period of seven months, and another for twenty-one months due to carcinoma of the pancreas One patient with secondary biliary cirrhosis due to carcinoma of the pancreas had clinical obstructive jaundice for only four months

Jaundice obviously is the most prevalent initial symptom in patients with eventual secondary biliary cirrhosis In most instances, obstructive jaundice in this condition due to benign lesions was intermittent and prolonged in contrast to unremitting, progressive obstructive jaundice due to neoplastic lesions Jaundice occurred within several weeks to nine months in patients with postoperative stricture of the common bile duct In Donaldson's series of 87 biliary strictures, obstructive jaundice occurred within the first five postoperative days in 40 per cent of the cases[21] Many of these cases of strictures had had several abdominal operations attempted for relief of the biliary obstruction. One case of secondary biliary cirrhosis with esophageal varices had had four reconstructive operations The rate of recurrence of these strictures is very high, amounting to as much as 62 per cent (Table III) [15,16 23]

The eventual symptoms of secondary biliary cirrhosis are listed in Table IV. In contrast to primary biliary cirrhosis, secondary biliary cirrhosis occurs in an older age group in both sexes. Ex-

TABLE III
INCIDENCE OF INITIAL SYMPTOM IN SECONDARY BILIARY CIRRHOSIS
(6 females, 6 males, youngest age, 18, oldest age, 72, mean age, 59)

	Cases
Jaundice	7
Fever and chills	2
Abdominal pain	1
Abdominal pain and jaundice	1
Hematemesis	1

phageal hemorrhage from varices in 1 and 4 cases, respectively, palpable liver in 21 and 22 cases, respectively, and palpable spleen in 7 and 11 cases, respectively. In 27 cases of advanced secondary biliary cirrhosis, spider angioma was present once and xanthomatosis in 2 cases. Generally, the physical stigmata of portal cirrhosis, excepting hepatosplenomegaly, are found less frequently in patients with secondary biliary cirrhosis. Twenty two of one hundred twenty two cases of stricture of the common bile duct reported by Cole and his associates demonstrated evidence of portal hypertension.[14] They recommended splenorenal shunt after preliminary repair of the common bile duct, splenectomy for hypersplenism in patients with secondary biliary cirrhosis and reconstruction of the common bile duct.[23,4]

LABORATORY FEATURES

The pertinent laboratory data of secondary biliary cirrhosis are listed in Table VI and re-emphasize the indistinguishable features from those in primary biliary cirrhosis. The predominance of leukocytosis is probably due to secondary cholangitis. These laboratory tests are indicative of biliary obstruction, and only until secondary biliary cirrhosis is well advanced do tests suggestive of hepatocellular dysfunction become abnormal. The prothrombin time, however, is increased early in most cases of secondary biliary cirrhosis, and, as expected, non variceal hemorrhages are a common finding.[8] Hypoprothrombinemia in these cases is due to the impaired absorption of the fat-soluble vitamin K as result of biliary steatorrhea. In all types of biliary cirrhosis, serum mucoprotein is invariably elevated. The serum iron, serum cholinesterase, and serum transaminase are usually within the normal limits. Greenspan and Dreiling noted increased levels of serum mucoprotein in 98 per cent of 125 patients with biliary tract obstruction.[33] Xanthomatosis, melanosis, hypercholesterolemia, and hyperphospholipidemia were found in 1 patient with secondary biliary cirrhosis. Ahrens and his associates found generalized xanthomatosis associated with established chronic biliary obstruction in 24 cases in the literature between 1851 and 1950 and added 2 cases.[1] The association of xanthomatosis with abnormal elevations of total cholesterol, phospholipids, and total



FIG 11a Needle biopsy of liver Secondary biliary cirrhosis (Table X) Several days later a pancreaticoduodenectomy was performed for an adenocarcinoma of the head of the pancreas There was no evidence of metastasis or malignant infiltration. The results of the cholangiogram were normal. (H & E, X60).
FIG 11b Needle biopsy of the liver of same patient sixty-five days later Metastatic adenocarcinoma of liver (H & E, X60)

phageal hemorrhage from varices in 1 and 4 cases, respectively, palpable liver in 21 and 22 cases, respectively, and palpable spleen in 7 and 11 cases, respectively. In 27 cases of advanced secondary biliary cirrhosis, spider angioma was present once and xanthomatosis in 2 cases. Generally, the physical stigmata of portal cirrhosis, excepting hepatosplenomegaly, are found less frequently *in patients with secondary biliary cirrhosis*. Twenty two of one hundred twenty two cases of stricture of the common bile duct reported by Cole and his associates demonstrated evidence of portal hypertension[16] They recommended splenorenal shunt after preliminary repair of the common bile duct, splenectomy for hypersplenism in patients with secondary biliary cirrhosis, and reconstruction of the common bile duct.[24]

LABORATORY FEATURES

The pertinent laboratory data of secondary biliary cirrhosis are listed in Table VI and re-emphasize the indistinguishable features from those in primary biliary cirrhosis. The predominance of leukocytosis is probably due to secondary cholangitis. These laboratory tests are indicative of biliary obstruction, and only until secondary biliary cirrhosis is well advanced do tests suggestive of hepatocellular dysfunction become abnormal. The prothrombin time, however, is increased early in most cases of secondary biliary cirrhosis, and, as expected, non variceal hemorrhages are a common finding.[8] Hypoprothrombinemia in these cases is due to the impaired absorption of the fat soluble vitamin K as result of biliary steatorrhea. *In all types of biliary cirrhosis*, serum mucoprotein is invariably elevated. The serum iron, serum cholinesterase, and serum transaminase are usually within the normal limits. Greenspan and Dreiling noted increased levels of serum mucoprotein in 98 per cent of 125 patients with biliary tract obstruction.[37] Xanthomatosis, melanosis, hypercholesterolemia, and hyperphospholipidemia were found in 1 patient with secondary biliary cirrhosis. Ahrens and his associates found generalized xanthomatosis associated with established chronic biliary obstruction in 24 cases in the literature between 1851 and 1950 and added 2 cases.[3] The association of xanthomatosis with abnormal elevations of total cholesterol, phospholipids, and total



Fig 12 Roentgenogram of small intestine Hepatobiliary steatorrhea, secondary biliary cirrhosis due to recurrent postoperative stricture of common bile duct, three hour film, hypomotility, moulage pattern, segmentation, distended loops of intestine



Fig 15 Operative cholangiogram from a patient with obstructive jaundice Secondary biliary cirrhosis, note marked distention of extrahepatic biliary tract and a gallstone (arrow) lodged at ampulla of Vater



FIG 12 Roentgenogram of small intestine Hepatobiliary steatorrhea, secondary biliary cirrhosis due to recurrent postoperative stricture of common bile duct, three hour film; hypomotility, moulage pattern, segmentation, distended loops of intestine

8 of the 10 cases[84,79] Eder and his associates found that in some cases of obstructive jaundice and in biliary cirrhosis, there are at least two types of abnormal lipoproteins[77] One is found in Fraction IV, V and VI, and the other in Fraction I and III Removal of the biliary obstruction found these abnormal lipoproteins replaced by lipoproteins of normal composition.

TABLE VII
CAUSES OF DEATH IN 5 CASES OF SECONDARY BILIARY CIRRHOSIS

	Cases
Immediate cause	
Hepatic insufficiency	3
Carcinoma of pancreas	1
Acute peritonitis (p o)	1
Contributing cause	
Pneumonia	2
Gastrointestinal hemorrhage	1
Postoperative shock	1
Thrombosis of portal vein	1
Congestive heart failure	1
Intrahepaticolithiasis	2
Chronic pancreatitis	1

PRINCIPLE AND CONTRIBUTING CAUSES OF DEATH

The immediate and contributing causes of death in 5 cases of secondary biliary cirrhosis are listed in Table VII. The principal causes of death in Doehlert s series of secondary biliary cirrhosis, most of which occurred postoperatively, were hepatic insufficiency, 12 cases, hemorrhage from esophageal varices, 2 cases, hemorrhage from sources other than varices, 17 cases, renal insufficiency, 7 cases, and peritonitis, 11 cases[30] In a series of 93 cases of biliary cirrhosis reported by Schmitz and Sinaiko, the immediate causes of death were bronchopneumonia, 30 cases, peritonitis, 16 cases, a combination of these, 8 cases, and terminal hemorrhage, 13 cases[134] Experimentally, hepatic failure has been the cause of death in animals with complete biliary obstruction[49]

TREATMENT

Surgical decompression of biliary obstruction may produce marked reversal of the clinical and biochemical findings in secondary biliary cirrhosis Portal hypertension may subside as evidenced by a fall in portal venous pressure, diminution of splenomegaly and endoscopic disappearance of esophageal varices Jaundice slowly diminishes and hepatic function improves steadily

lipids in the blood in cases of secondary biliary cirrhosis is similar to this condition in primary biliary cirrhosis Hepatobiliary steatorrhea was present and a nutritional deficiency pattern in the small intestine was observed in a case of postoperative stricture of the common bile duct (Figs. 11, 12).

TABLE VI
LABORATORY DATA IN 12 CASES OF SECONDARY BILIARY CIRRHOSIS

	Cases
Leucocytosis	10
Leucopenia	none
Thrombocytopenia	none
Normochromic, normocytic anemia	1
Hypochromic, microcytic anemia	1
Hypoalbuminemia	4
Hyperglobulinemia	5
Abnormal cephalin-cholesterol flocculation	4 (8)*
Abnormal thymol turbidity	2 (4)*
Abnormal zinc sulfate turbidity	2 (2)*
Elevation plasma alkaline phosphatase	7 (8)*
Normal serum cholinesterase	2 (2)*
Elevated serum mucoprotein	2 (2)*
Normal serum iron	2 (2)*
	7
	6 (8)*
	1 (4)*
	56
Average direct total serum bilirubin	8 73
	13 02
Steatorrhea and azotorrhea	1 (1)*
Nutritional deficiency roentgenographic pattern small intestine	1 (1)

*Number of cases studied

Because of the impairment of the excretory function of the liver in secondary biliary cirrhosis or, in fact, in any case of biliary obstruction, the diagnostic use of intravenous cholangiography *is restricted* [2,5,32] *Percutaneous transhepatic* cholangiography has been recommended to demonstrate the patency of the biliary tract, but there is a risk of bile-peritonitis [40,66] Electrophoresis of serum proteins in 3 cases of secondary biliary cirrhosis disclosed hypoalbuminemia in all, normal fractional globulins in 2, and mild elevation of beta and gamma globulins in 1. Sterling and Ricketts studied the electrophoretic pattern in 10 cases of secondary biliary cirrhosis and found diminution of the albumin fraction and elevation of beta globulin due to increased lipoprotein in all cases, and elevation of the gamma globulin in



Fig 15 Intravenous cholangiogram Radiolucent choledocholithiasis mild obstructive jaundice had recurred, and the results of the hepatic flocculation tests were normal No morphological evidence of cirrhosis, no marked dilatation of common, hepatic, and intrahepatic bile ducts

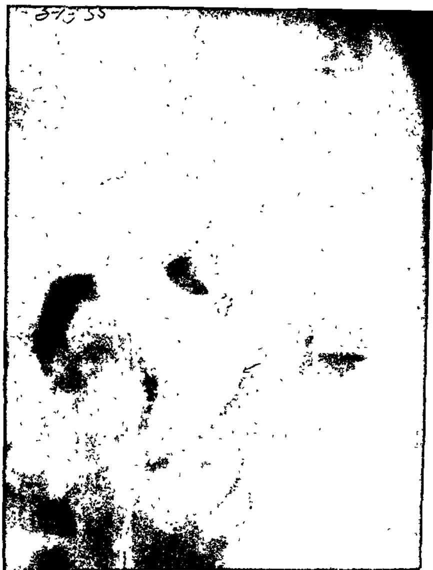


Fig 14 Postoperative cholangiogram through a T-tube Choledocholithiasis (arrow) The patient's main complaints were mild biliary colic and despite no physical findings, the results of the hepatic battery of tests were normal While some regions of the extrahepatic biliary tract appear dilated, this incident suggests the benefit derived from routine operative diagnostic cholangiography in cases of obstructive lesions of the biliary tract despite lack of clear-cut indications



Fig 15 Intravenous cholangiogram Radiolucent choledocholithiasis mild obstructive jaundice had recurred, and the results of the hepatic flocculation tests were normal No morphological evidence of cirrhosis, no marked dilitation of common, hepatic, and intrahepatic bile ducts

LABORATORY DATA in a CASE of SECONDARY BILIARY CIRRHOSIS with CUTANEOUS XANTHOMATOSIS due to POSTOPERATIVE STRICTURE of COMMON BILE DUCT
(DISAPPEARANCE of XANTHOMAS at 21 MONTHS)

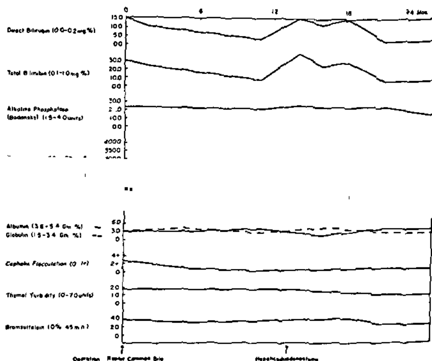


Fig 16

In 1 case of secondary biliary cirrhosis there was no evidence clinically or biochemically of this condition 56 days after choledocholithotomy (Table VIII) In another case due to carcinoma of the pancreas, pancreaticoduodenectomy temporarily improved hepatic function (Tables IX, X). In a case of secondary biliary cirrhosis with xanthomatosis due to postoperative stricture of the common bile duct, hepaticoduodenostomy produced a clinical remission, decreased fractionated serum lipids, and disappearance of cutaneous xanthomatosis (Figs 16, 17, 18). Cholangiograms should be routinely obtained, preferably during the course of the operative procedure or later through a T-tube, in patients with secondary biliary cirrhosis (Figs 13, 14, 15).[47,49] In addition, it

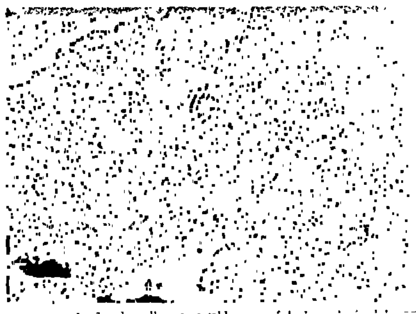




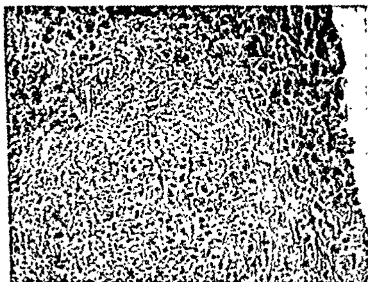
FIG 17a Xanthoma planum in creases of fingers and palms Patient had secondary biliary cirrhosis No other areas of xanthomatosis Same case as Figure 16 this photograph was just before the hepaticoduodenostomy

FIG 17b Considerable resolution three months following hepaticoduodenostomy

must be absolutely certain that obstructive jaundice has not been induced with icterogenic drugs (Chapter 8).[55] Residual or recurrent choledocholithiasis, not frequently encountered when an adequate choledochostomy and operative cholangiogram are performed, may produce eventual secondary biliary cirrhosis (Table XI).[14 16 26,31,76,95,85] The medical treatment of clonorchiasis is unsatisfactory. Gentian violet in oral or intraduodenal dose of 0.06 gm three times daily before meals for 20 to 30 days has been recommended. This agent may be employed intravenously in 1 per cent solution, 20 cc. are prescribed as the first dose and 30 cc for the next three days.[78] Fuadin is the drug of second choice. Emetine hydrochloride in a dose of 60 mg. daily for seven to ten days is the drug of choice in the treatment of fascioliasis.



biliary cirrhosis (H & E, X60).



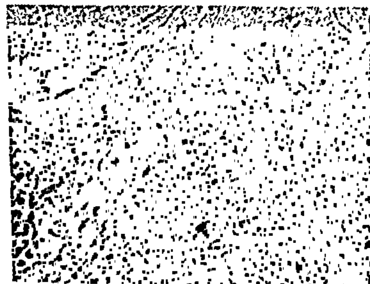


TABLE VIII

Laboratory Data on Twenty one Year Male with Secondary Biliary Cirrhosis due to Choledocholithiasis

(Painless jaundice for six months, cutaneous melanosis, hepatomegaly 8f, splenomegaly 1f)

Laboratory Data	*Normal*	Days *1*	*19*	*21*	*56*
Bilirubin mg /100 cc.	D 0 0 0 2 / T 1 0-1.5	4 46 / 8 30	1.22 / 2 73	1 44 / 3 20	0 17 / 1 77
Alk phosphatase, Bodansky units	2 4	20 6	8 6	5.2	3.2
Cholesterol mg /100 cc	120 300	491	—	—	213
Cholesterol esters mg /100 cc	(70 80% of total)	219	—	—	129
Phospholipids mg /100 cc	110 250	470	—	—	147
Neutral fat mg /100 cc	25 600	321	—	—	276
Total lipids mg /100 cc	450 1,100	1,350	—	—	636
Bromsulfalein dye retention, % 45 min	0	—	—	—	0
Serum albumin gm /100 cc	3 6 5 4	—	—	—	4 5
Serum globulin gm /100 cc	1.5-3 4	—	—	—	2.2
Ceph floc 48 hr	0 1+	0	—	—	7
Thymol burbidity, units	0 7	1 1	—	—	0 9
Zinc sulfate turbidity, units	3.5 10.5	2.5	—	—	3 2
Prothrombin time, %	100	43 6	—	—	100
Total protein, gms /100 cc	6 8	7 2	—	—	—
Albumin, gms /100 cc	3 8-4 6	3 4	—	—	—
Alpha1 globulin	0.2 0.5	0.5	—	—	—
Alpha2 globulin	0 5-1 2	1 2	—	—	—
Beta globulin	0 75 1 3	1 1	—	—	—
Gamma globulin	1 0 1 4	1 0	—	—	—
Sedimentation rate mm /hr Westergren	0 10	52	—	—	—
Urine urobilinogen mg /24 hr	1-4	0 8	—	—	2 2
Fecal urobinogen mg /24 hr	100-250	187	—	—	227
		Operation	Cholecystectomy Choledocholithotomy T tube drainage for 5 weeks		

TABLE IX

Results of Serial Laboratory Tests from a Patient With Secondary Biliary Cirrhosis Due to Carcinoma of the Pancreas

Test	*Normal Value*	*1 mo*	*6 mo*	*16 mo*
Blood hemoglobin gm /100 cc	(12 15)	–	11 9	11 3
Blood leukocytes cu mm.	(5,500 7,500)	–	6 000	8 700
Erythrocyte sedimentation rate (Westergren)	(0 20)	–	105	116
Serum bilirubin mg /100 cc	(D T 0 2 1 5)	3 4 / 4 8	11 1 / 21 5	10 7 / 18 8
Alkaline phosphatase, Bodansky units	(1 5 4 0)	–	17 2	61 9
Blood glucose, mg /100 cc	(55 90)	–	65	–
Serum albumin/globulin gm /100 cc	(3 5 2 5)	4 0 / 2 2	3 4 / 2 0	3 5 / 2 3
Cephalin-cholesterol flocculation 48 hours.	(0 1+)	3+	0	3+
Thymol turbidity units	(0 7)	–	4 3	2 3
Zinc sulfate turbidity units	(3 5 10 5)	–	2 5	7 4
Plasma cholesterol, mg /100 cc	(150 250)	–	692	680
Cholesterol esters mg /100 cc	(70 80% of total)	–	676 (95%)	170 (25%)
Phospholipid (lecithin), mg 100 cc	(110 250)	–	1,520	1 169
Neutral fat, mg /100 cc	(25 600)	–	–	97
Total lipids, mg /100 cc	(450 1 100)	–	2,530	2,085
Serum mucoprotein, mg /100 cc	(10 13)	–	18 2	19 1
Urobilinogen quantitative, mg				
(urine, 24 hours, 1 4)		–	0 8	0 5
(stool, 24 hours, 50-300)		–	18 5	31 8
Serum iron mg /100 cc	(70 185)	–	56	104
Stool, quantitative fat, 24 hours gm	(1 5)	–	–	12 0
Stool, quantitative nitrogen, 24 hours gm	(1 2)	–	–	4 1
		Before abdominal laparotomy		

TABLE X
LABORATORY DATA IN A PATIENT WITH SECONDARY BILIARY CIRRHOSIS
DUE TO ADENOCARCINOMA OF PANCREAS

Laboratory Tests	*Normal*	*Postoperative Whipple Pancreaticoduodenectomy* 0 mo	2 mo	12 mo	22 mo	65 mo
Serum bilirubin, Direct	0.2	10.16	7.42	1.98	1.12	7.86
mg/100ml Total	1.5	17.40	13.06	3.53	2.18	13.51
Alk phosphatase, units Bodansky	2-4	29	—	5.5	10	8.2
BSP % 45 min	0	—	—	—	12	—
Blood cholesterol mg/100 ml	120-300	362	—	312	—	312
Serum albumin gm/100 ml	3.6-5.4	3.2	3.0	2.4	3.4	3.4
Serum globulin gm/100 ml	1.5-3.4	3.5	3.1	2.7	3.1	3.9
Blood cholesterol esters mg/100 ml	125-180	172	—	161	—	147
Glucose mg/100 ml	55-90	118	123	—	94	99
Thymol turbidity	0-7	17	—	7.4	6.4	21.8
Ceph floc 48 hr	0 to 1+	0	—	1+	0	3+
Prothrombin % of normal (67-100%)	100	46	—	67	67	85
Quantitative stool fat, 24 hrs	1.5 gm	17.9 gm	—	—	—	24.4 gm
Quantitative stool nitrogen, 24 hrs	1-2 gm	5.7 gm	—	—	—	6.2 gm
Urine urobilinogen, mg 24 hur	(1-4)	—	—	—	12	—
Fecal urobilinogen, mg, 24 hr	(50-300)	—	—	—	24	—
Liver biopsy	—	Biliary Cirrhosis	—	—	—	Biliary Cirrhosis; Metastatic Adenocarcinoma

TABLE XI

RESULTS OF SERIAL LABORATORY TESTS FROM A PATIENT WITH CHOLEDOCHOLITHIASIS AND POSTOPERATIVE STRICTURE OF COMMON BILE DUCT, PROGRESSION FROM CHOLESTATIC HEPATIC DISEASE TO SECONDARY BILIARY CIRRHOSIS

	Normal Values	*1 yr.*	*3½ yr.*	*6 yr.*
Blood leucocytes, cu mm	(3,500 7,500)	9,800	5,650	10,300
Serum bilirubin, mg /100 cc.	(D/T 0.2/1.5)	1.1/2.2	13.1/18.5	3.3/5.5
Alkaline phosphatase, Bodansky units	(1.5 4.0)	8.4	22.4	11.2
Plasma cholesterol, mg /100 cc	(130 250)	189	279	176
Cholesterol esters, mg /100cc.	(70 80% total)	127	151	82
Serum albumin/globulin, gm /100 cc	(3.5/2.5)	1.0/3.6	2.4/4.0	3.2/3.6
Bromsulfalein dye retention, 45 min	(0 5%)	29	—	—
Cephalin cholesterol flocculation, 48 hr	(0, 1+)	2+	2+	4+
Thymol turbidity, units	(0 7)	—	8.1	13.3
Zinc sulfate turbidity, units	(3.5 10.5)	—	13.2	14.8
Serum mucoprotein, mg /100 cc	(10 13)	—	—	18.2
Prothrombin time	(100%)	73	70	35*
Serum transaminase (SGO-T)	33 118 micro-moles/100cc	—	—	218
Erythrocyte sedimentation rate (Westergren)	(0 20)	—	—	120
		Choledochostomy	Choledocholithotomy, duodenocholedochostomy	Hepaticoduodenostomy

*Operative procedures without parenteral vitamin K

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Chapter 10

HEMOCHROMATOSIS

INTRODUCTION

A CASE OF HEMOCHROMATOSIS was first described by Trousseau in 1865.[127] The disease was named "haemochromatosis" by von Recklinghausen in 1889, "pigmentary cirrhosis" by Troisier in 1871 and "bronze diabetes" by Hanot and Schachmann in 1886.[59,124,125] In 1935, Sheldon reviewed the medical literature of the world and compiled a classic monograph comprising detailed and authentic reports of 311 cases of hemochromatosis.[113] He regarded this disease as an inborn error in the metabolism of iron, but his study did not reveal any evidence that hemochromatosis was a secondary lesion produced by hemosiderin or that hemochromatosis resulted from the destruction of blood, from the action of toxins or from malnutrition.

In the past few years, there has been a renewed interest in disorders of iron metabolism and pathological conditions in which abnormal amounts of iron are deposited in various tissues of the body. The availability and increased therapeutic use of transfusions of blood together with the introduction of improved diagnostic techniques such as needle biopsy of the liver, radioisotopic-iron absorption studies, and determinations of the serum iron, iron-binding globulin and its saturation value, have provoked interested concern among physicians about possible cytotoxic action of exogenously administered iron and its deleterious effect upon the function of certain vital organs, including the liver. As a consequence, the conspicuous gap in research on hemochromatosis which followed the publication of Sheldon's monograph was interrupted in 1945 with scientific reports throughout the world on various aspects of iron-storage disease, hemochromatosis and hemosiderosis. These included clinical and pathological investigations of these conditions, studies with experimental animals, the discovery of an obscure association of various chronic anemias and hemochromatosis, studies of iron metabolism, in-

cluding those employing radioactive iron, the specific treatment of hemochromatosis by multiple phlebotomy and the investigation of certain chelating agents which have the property of mobilizing iron from the tissues.

A clinicopathological classification of iron storage diseases was proposed in 1955 which delineated hemochromatosis from hemosiderosis.[78]

IRON-STORAGE STATES

1. Hemochromatosis (a specific disease)
   A. Primary or Classical
      1. Heredito-familial
   B. Secondary (associated with chronic anemias)
2. Hemosiderosis (a pathological condition)
   A. Malnutritional
      1. "Cytosiderosis"
   B. Exogenous (excessive blood transfusions, intravenous administration of iron or prolonged oral use of iron)
   C. Associated with various refractory aplastic megaloblastic or hemolytic anemias

ETIOLOGY

The cause and pathogenesis of hemochromatosis are unknown. Malnutrition, alcoholism, cirrhosis, degeneration of erythrocytes, toxins, intoxication with heavy metals including exogenously administered iron, diabetes mellitus, congenital metabolic errors, and various endocrine disturbances have been implicated as possible etiological factors.[61] Althausen and his associates have demonstrated that malnutrition alone is not a basic causative factor.[1-3] Sheldon considered hemochromatosis to be a congenital, inborn error of iron metabolism.[115] Experimentally, it has been found that a diet deficient in calcium but fortified by phosphorus and iron produces hemosiderosis but not hemochromatosis.[74,123]

Granick has shown that iron is absorbed normally in the region of the duodenum.[56,57] Iron is absorbed in the ferrous state, and absorption is decreased by a diet high in phosphorus content, and increased in iron-deficiency anemias and hemochromatosis and by ingestion of ascorbic acid with iron.[100] Apoferritin, a specific protein, binds iron to the plasma. The apo-

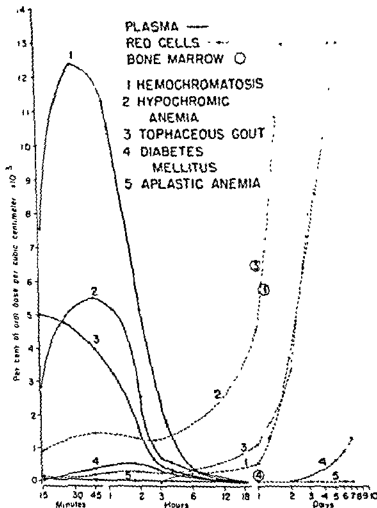


FIG 1 Investigational data of radioisotope iron intestinal absorption demonstrating the *amount* and retention of Fe^{59} in hemochromatosis and other conditions (Kleckner *et al* — J A M A — April 23, 1955)

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four phlebotomized patients who had been administered oral Fe^{59}. Twenty one patients ill with a variety of diseases including anemia, portal cirrhosis, and diabetes mellitus served as control subjects. As shown in Figure 1, significant elevations of radioiron were demonstrated in the plasma from fifteen minutes to one hour after ingestion. Levels of radioiron were significantly higher in all patients with hemochromatosis than the levels obtained in the control subjects. This independent finding confirms in part the original radioisotopic data of Balfour and others.[6] Significant levels of urinary Fe^{59} were never demonstrated in any of the patients excepting one patient with hemochromatosis, in whom it was found on the day following the test. Further determinations disclosed that fecal Fe^{59} levels were consistently and inversely related to plasma Fe^{59} levels. For example, patients with low amounts of fecal Fe^{59} usually had an elevated level of plasma Fe^{59}. In some cases, however, fecal Fe^{59} was decided increased ten days later. These studies support the contention that immediate absorption of Fe^{59} occurs in treated cases of hemochromatosis. Recent studies by Chodos and others indicate that patients with hemochromatosis following venesections absorb considerably more radioactive iron than healthy subjects but in untreated patients with hemochromatosis, there is little absorption of radioactive inorganic iron and even less food iron.[20,21] These studies demonstrate that excessive absorption of iron is a major pathogenic factor in the production of hemochromatosis. However, they do not explain in what manner excess iron produces the typical pathological lesions of hemochromatosis (Table I).

PRIMARY OR CLASSIC HEMOCHROMATOSIS

This type of hemochromatosis has been adequately described in several reports.[1,18,21,37,39,52,68,73,74,115,114] Clinically, it occurs almost exclusively in men in the fifth or sixth decade of life in whom hepatomegaly, diabetes mellitus, pigmentation of the skin, sexual hypoplasia or various combinations of these manifestations are clinical findings. Patients who have hemochromatosis may have sudden or slow development of the clinical manifestations of this disease.

ferritin-ferritin system has been postulated to regulate the absorption of iron from the intestinal tract.[121] Finch and Finch have compartmentalized the total iron in the normal human body into four fractions (1) the largest portion of iron in the body is the erythrocyte, (2) excess iron is deposited in various tissues in a soluble form, ferritin, or an insoluble form, hemosiderin, readily available for use by the erythrocyte; (3) certain iron-pyrol-protein complexes in various tissues such as myoglobin, cytochrome, and catalase present usually in a static state, (4) plasma iron bound to a beta-1 globulin, siderophilin, which transfers iron to various tissues.[8,41 43]

Radioactive iron absorption studies have demonstrated that there is an increased absorption of iron in hemochromatosis[6 13 14 25 36 37,41 43,76,79 99] Radioiron absorption uptake was studied in

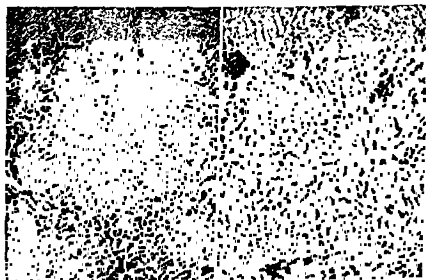


Fig 2 Liver in hemosiderosis Iron in Kupffer cells and in hepatic cells at periphery of lobule (Prussian Blue, X60) (Courtesy, Kleckner, Baggenstoss, and Weir—*Am J Clin Path — August, 1955*)

Fig 3 Liver in severe hemosiderosis as the result of 291 transfusions of blood Iron in all hepatic cells, in clumps of phagocytic cells, and in widened portal tracts, the vascular relationships are normal and regenerative nodules are absent (Prussian Blue, X110). (Courtesy, Kleckner, Baggenstoss and Weir—Am J Clin Path —August, 1955).

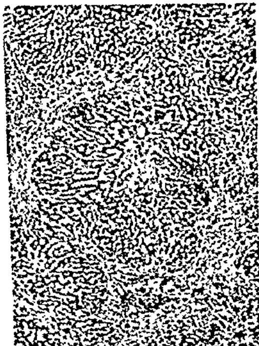


FIG 4 Liver in severe hemosiderosis with fibrosis of portal tracts mimicking cirrhosis of hemochromatosis However, there are normal vascular relationships, undisplaced central vein and no actual regenerative nodules (H & E. X45) (Courtesy, Kleckner, Biggenstoss, and Weir—Am J Clin Path—August, 1955)

FINDINGS

It is unusual to find abnormalities in the bromsulphalein and hepatic flocculation tests early in the clinical course of hemochromatosis A surprising lack of correlation has been shown to exist between impaired hepatic function and histological evidence of a type of cirrhosis. In fact, hepatomegaly in association with normal or minimally abnormal hepatic function tests should alert one of the possibility of hemochromatosis In seven living patients with hemochromatosis, it has been noted that the longer the duration of the disease in the younger patient, the more

TABLE I
SCHEMATIC CORRELATION
OF
PATHOLOGICAL, CLINICAL AND THERAPEUTIC ASPECTS
OF
HEMOCHROMATOSIS

Treatment	*Death*	*Pathology*	*Pathogenesis*	*Clinical*	*Laboratory*
1. conventional	1 hepatic insufficiency or hepatoma	1 cirrhosis	1 malnutrition (protein) 2 congenital 3 hepatitis 4 pancreatitis	1 hepato splenomegaly 2 pigmentation of skin 3 endocrine imbalance testicular atrophy, etc 4 pain 5 ascites and edema	1. abnormal hepatic function tests 2 hypo albuminemia
2 conventional	2 diabetes mellitus	2 pancreatic fibrosis	1 alcohol 2 hepatic damage	1 diabetes mellitus 2. pancreatic diarrhea 3 steatorrhea	1. hyperglycemia 2 hyperlipemia
3 phlebotomy chelating agents	3 congestive heart failure	3 iron storage disease (liver, heart, spleen, stomach, endocrine glands, pancreas, lymph nodes)	1. excessive absorption of iron a) malnutrition b) congenital c) exogenous (?)	1 none	1. elevated serum iron 2 saturated of iron-binding globulin 3. abnormal EKG



FIG. 5b Sagittal section of a liver with hemochromatosis and a circumscribed hepatoma

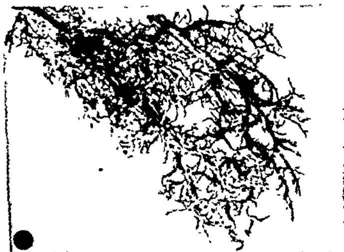


FIG. 5c Portion of hepatic cast in hemochromatosis with hepatoma (X3) The small light bunches represent the vessels of tumor nodules and are derived from the hepatic artery, the darker portal vein does not appear to enter into these nodules (Courtesy, Mann, J D, and Baggenstoss, A. H—Gastroenterology—December, 1955)

abnormal the tests of hepatic function will be. Similarly, in three cases, improvement in the values of these tests followed abstinence from alcohol and therapy with a high-calorie diet, yeast, and vitamins Two additional cases had improvement in their hepatic function test with this therapeutic regimen and multiple massive phlebotomy The newer hepatic function tests, such as, serial serum cholinesterase and mucoprotein determinations, also reflect normal values except during the terminal course of this disease. Recently, moderately elevated values of serum transaminase were found in an early and moderately advanced case of hemochromatosis. Electrophoresis of serum proteins now has been done in 5 living patients, and, while not diagnostic, disclosed in 1 case slight elevation of beta and gamma globulins Table VI shows the average laboratory determinations in a large group of advanced cases of hemochromatosis Once hepatocellular function becomes impaired late in the disease, abnormalities may be reflected in hepatic function tests The cephalin-cholesterol flocculation test appears to be the most sensitive indicator of hepatic dysfunction of all the flocculation or turbidity tests None of these laboratory tests is particularly helpful in arriving at a diagnosis of hemochromatosis but are valuable in following the clinical course of the patient This disease usually occurs in adult males and postmenopausal or amenorrheic females In half of the cases, diabetes mellitus had been present for a year prior to death Abdominal pain was recognized as an important symp-



FIG. 5a Liver in hemochromatosis Sagittal section cirrhosis and infiltrating hepatoma

clinical diagnosis could be established (Table II) These patients died of causes unrelated to hemochromatosis

Pathologically, a finely granular cirrhosis, fibrosis of the pancreas, testicular atrophy and visceral discoloration are gross findings An abundance of hemosiderin is evident in the liver, heart, gastric glands and endocrine glands (Tables III, IV, V). Death is usually caused by congestive heart failure or hepatic insufficiency Not uncommonly, a hepatoma complicates hemochromatosis (Fig 5)[7] Warren and Drake (Fig 9b) reported an unusually high incidence of hepatoma in their cases (18.9 per cent)[10] In the present series, there were only 3 cases of primary carcinoma, an

TABLE III
SIGNIFICANT DIFFERENCES IN FINDINGS BETWEEN 26 CASES OF *PRIMARY HEMOCHROMATOSIS* AND
20 CASES OF TRANSFUSIONAL HEMOSIDEROSIS

	Hemochromatous Cases	*Transfusional Hemosiderosis, Cases*
Clinical findings		
Sex		
Male	25	11
Female	1	9
Diabetes mellitus	15	0
Pigmentation of skin	18	2
Enlarged liver	19	3
Testicular atrophy	8 (22)	0
Anemia	1	20
Ascites	19	8
Hepatic coma	9	1
Congestive cardiac failure	9	2
Pathologic findings		
Cirrhosis of liver	26	1
Atrophy of pancreas	18	0
Deposits of hemosiderin in		
Epithelium of hepatic bile ducts	23	8
Pancreas	21	5
Gastric glands	11 (15)	2
Myocardium	19	2
Adrenal gland	22 (25)	4 (16)
Medulla	2 (25)	0 (16)
Epithelium of thyroid gland	17 (20)	3 (14)
Parathyroid gland	6 (6)	1 (5)
Prostate gland		
Epithelium	9	0
Connective tissue	8	0
Testes		
Seminiferous tubules	3	1
Interstitial tissue	9	1

Numbers in parentheses indicate number of cases in which information was available when such data were not recorded in every case of the series
(Kleckner, Baggenstoss and Weir, Am J Clin Path Aug 1955)

TABLE II

CLINICAL FINDINGS IN 35 PATIENTS (34 MEN AND 1 WOMAN) WITH HEMOCHROMATOSIS, THE AGE AT DEATH WAS 30 TO 80 YEARS (AVERAGE 55) AND THE DURATION OF DISEASE 1 TO 25 YEARS (AVERAGE 4 YEARS)

Symptoms at Onset	*No of Cases*
Weakness	14
Diabetes	8
Ascites and edema	4
None	3
Pigmentation of skin	2
Abdominal pain	2
Weakness and dyspnea	1
Jaundice and ascites	1

Eventual Symptoms	*No of Cases*
Diabetes	23
Dyspnea	20
Alcoholism	18
Abdominal pain	18
Indigestion	16
Gastrointestinal hemorrhage	5
Diarrhea	4
Peripheral neuritis	2
Epistaxis	2

Physical Findings on Hospital Admission	*No of Cases*
Edema	29
Enlarged liver	28
Loss of weight	25
Pigmentation of skin	24
Ascites	23
Enlarged spleen	13
Jaundice	13
Enlarged heart	10
Pleural effusion	10
Testicular atrophy	9
None	7
Loss of hair	6
Spider angioma	5
Palmar erythema	3
Gynecomastia	3
Arterial hypertension	3
Caput medusae	1
Purpura	1

Complications	*No of Cases*
Esophageal varices	8
Bronchopneumonia	7
Ruptured esophageal varices	3
Hepatoma	3
Cholelithiasis	3
Carcinoma (rectum)	1
Carcinoma (lip)	1
Gastric ulcer	1
Duodenal ulcer	1
Acute glomerulonephritis	1
Portal thrombosis	1
Chronic pancreatitis	1
Hemorrhagic gastritis	1
Cerebral thrombosis	1
Chronic pericarditis	1

Causes of Death	*No of Cases*
Hepatic insufficiency	16
Congestive heart failure	11
Septicemia	2
Renal insufficiency	1
Bronchopneumonia	1
Tuberculous peritonitis	1
General peritonitis	1
Pulmonary edema	1
Acute circulatory collapse	1

(Kleckner *et al*, J A M A, April 23, 1955)

tom of hemochromatosis[34] Loss of weight ranged from 10 to 55 pounds (4.5 to 25 kg.). Pigmentation appears in the exposed areas of the body before the skin is involved generally, it is more commonly dark gray or slate or slate-colored than bronze.[23, 90] The disease in 8 patients with hemochromatosis was asymptomatic or had not reached a stage of development at which a definitive

TABLE V
HISTOLOGICAL DIFFERENTIATION OF HEMOCHROMATOSIS FROM TRANSFUSIONAL HEMOSIDEROSIS

Condition	Hemochromatosis	Transfusional Hemosiderosis
Laennec's cirrhosis	Always present	Absent
Hemosiderin in		
Liver		
Hepatic cells	Always present	Always present
Kupffer's cells	Always present	Always present
Bile ducts	Usually present	Often present
Stroma	Usually present	.. . . .
Pancreas		
Acini	Always present	Usually absent
Ducts	Always present	Usually absent
Islets	Usually present	Usually absent
Stroma	Usually present	.
Spleen	No absolute histological differentiation	
Lymph nodes, abdominal	Always present	Often present
Sweat glands and derma	Usually present	Often present
Renal tubules	Usually present	Often present
Gastric glands	Usually present	Usually absent
Myocardium	Usually present	Usually absent
Adrenal cortex	Usually present	Usually absent
Thyroid	Usually present	Usually absent
Parathyroid	Usually present	Often present

(Kleckner *et al.*, J.A.M.A., April 23, 1955)

therefore, hepatic function tests generally do not aid particularly in arriving at a definitive diagnosis Increased amounts of serum iron and saturation of the iron-binding globulin, demonstrated in most patients with hemochromatosis, are only presumptive evidence of hemochromatosis It has been found that the serum iron is high in patients with acute hepatitis, transfusional hemosiderosis, aplastic, hemolytic and myelophthisic anemias, post-necrotic cirrhosis, or portal cirrhosis with severe hepatic insufficiency[67 79 93 98 107 110] Finch and Finch have shown that the serum iron may be increased in asymptomatic relatives of patients with hemochromatosis (Table VI).[43]

Electrocardiographic abnormalities (in particular, auricular fibrillation, auricular flutter, low amplitude of the QRS complex, inversion of T waves, and bundle-branch block) are demonstrated frequently in patients with advanced hemochromatosis (Fig 18) [15 122] Generally, oral radioactive iron absorption tests reveal an increased immediate uptake of iron from the gastrointestinal

TABLE IV

Gross Pathological Findings in Forty-Two Patients with Hemochromatosis

Organ or Condition	*Findings*	*Weight*	
		Average	*Range*
Liver	Deep brown, finely granular cirrhosis	2,187 gm	750 5,227 gm
Spleen	Deep brown, hyaline perisplenitis, fibrosis	358 gm	85 545 gm
Heart	Deep brown	412 gm	256 574 gm
Ascites	Present in 26 cases	2,729 cc	100-20,000 cc
Esophageal varices	Present in 9 cases, ruptured in 4 cases	. . .	. . . . .
Kidneys	Normal color	384 gm *	217 725 gm *
Pleural effusion	Unilateral in 4 cases; bilateral in 30 cases	500 cc.	10-2,000 cc
Pancreas	Deep brown, atrophic in 28 cases	. .	
Testes	Atrophic in 10 cases	.	.
Thyroid and adrenals	Brown		.

*Combined weight

(Kleckner *et al*, J A M.A , April 23, 1955)

incidence of 11 5 per cent, which is greater than the incidence of carcinoma of the liver discovered at necropsy in a series of cases of cirrhosis of the liver [104] Edmondson and Steiner believed that this greater incidence results because individuals who have pigmentary cirrhosis live longer than those who have portal cirrhosis [39]

Observations and tests that may be helpful clinically in establishing the diagnosis of hemochromatosis include· (1) the demonstration of iron in the propria of the sweat glands and the upper part of the cutis of the skin; (2) the presence of hemosiderin in the gastric glands obtained by gastroscopic biopsy; (3) needle biopsy of the liver; (4) elevated values of serum iron, (5) saturation of the serum-iron-binding globulin; (6) intravenous iron-tolerance test; (7) intracutaneous ferric chloride test, and (8) the rate and amount of absorbable radioactive iron.[6 9,29,43,51,66 67,73,75-79,110 115,117,125] Laboratory studies frequently reveal minimal evidence of hepatic dysfunction despite the morphological findings in the liver characteristic of hem



FIG 6 Pancreas in hemochromatosis illustrating degeneration from fibrous connective tissue, fatty infiltration and atrophy

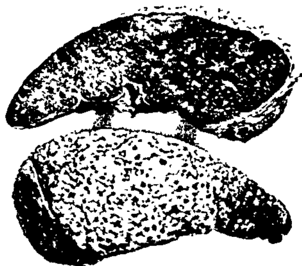


FIG 7 Spleen in hemochromatosis Weight 468 gm Sagittal section and surface; hypertrophy, chronic hyaline perisplenitis, chronic passive congestion and marked fibrosis

larity is the result of the small closely spaced nodules of regeneration (Fig. 9) These small nodules of regeneration and the narrow internodular zones of proliferated bile ducts and connective tissue are similar histologically to those observed in portal cirrhosis. In addition to the extensive deposits of hemosiderin, the cirrhosis associated with classic hemochromatosis differs from

TABLE VI
LABORATORY DATA IN FORTY-TWO PATIENTS WITH HEMOCHROMATOSIS

Determination	Patients Tested, No	Results*
Hemoglobin, gm./100 cc	42	10.4 (17.2-2.5)
Erythrocytes, millions/cu. mm	42	3.12 (5.01-0.87)
Leukocytes, per cu. mm.	42	8,125 (22,000-3,700)
Albuminuria	42	12
Erythrocyturia	42	2
Blood glucose, mg./100 cc	19	234 (476-98)
Blood urea, mg./100 cc	17	77 (178-28)
Serum bilirubin, mg./100 cc	20	
Direct		2.4 (11.3-0)
Indirect		1.9 (7.2-1.2)
Sedimentation rate (Westergren)	10	44 (77-22)
Retention of sulfobromophthalein sodium	11	Grade 1-4
Albumin-globulin ratio, gm./100 cc	18	2.5-5.5 to 2.9-2.6
Cholesterol, mg./100 cc	5	Low in 4
Cholesterol esters, mg. 100 cc	5	Low in 4
Erythrocyte smear	5	Macrocytosis
Prothrombin time, seconds (normal 17-19)	16	25 (20-23)
Cephalin-cholesterol flocculation	7	Abnormal in 4
Thymol turbidity	8	Abnormal in 2
Biopsy		
Skin	10	Iron in 8
Liver	8	Diagnostic in 8
Estrogens in urine	1	Normal
Blood phospholipids, mg./100 cc	1	167
Blood lipids, mg./100 cc	1	255
Electrocardiogram	24	Abnormalities present in 22†
Electrophoresis of serum protein	4	Normal

*Numbers in parentheses are highest and lowest values

†Low amplitude QRS in leads 1, 2, and 3, left ventricular strain, inverted T waves in leads 1, 2 and 3, auricular fibrillation (7 cases), and auricular flutter (1 case)

(Kleckner *et al*, J.A.M.A., April 23, 1955)

tract in patients with hemochromatosis, and that there is a greater uptake in these patients who are phlebotomized.[24, 25, 75, 70, 99] It has been found that needle biopsy of the liver, in particular, is the only reliable test available to diagnose hemochromatosis at the present time. If a finely granular cirrhosis and extensive deposits of iron are demonstrated histologically, the diagnosis of hemochromatosis is confirmed until disproved.

Inasmuch as the presence of cirrhosis of the liver is a reliable distinction between hemosiderosis and hemochromatosis, it is worthwhile to point out a few of the characteristics of this variety of cirrhosis (Figs. 2-5). The livers are generally larger than normal and are brown and finely granular (Fig. 8). The granu-



FIG. 6 Pancreas in hemochromatosis illustrating degeneration from fibrous connective tissue, fatty infiltration and atrophy

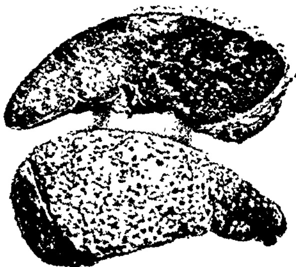


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Blood urea, mg /100 cc	17	77 (178 28)
Serum bilirubin, mg /100 cc	20	
Direct		2 4 (11,3 0)
Indirect		1 9 (7.2-1.2)
Sedimentation rate (Westergren)	10	44 (77-22)
Retention of sulfobromophthalein sodium	11	Grade 1 4
Albumin globulin ratio, gm /100 cc	18	2.5 5.5 to 2 9 2 6
Cholesterol, mg /100 cc	5	Low in 4
Cholesterol esters, mg/100 cc	5	Low in 4
Erythrocyte smear	5	Macrocytosis
Prothrombin time, seconds (normal 17-19)	16	25 (20 23)
Cephalin cholesterol flocculation	7	Abnormal in 4
Thymol turbidity	8	Abnormal in 2
Biopsy		
Skin	10	Iron in 8
Liver	8	Diagnostic in 8
Estrogens in urine	1	Normal
Blood phospholipids, mg /100 cc	1	167
Blood lipids, mg /100 cc	1	235
Electrocardiogram	24	Abnormalities present in 22†
Electrophoresis of serum protein	4	Normal

*Numbers in parentheses are highest and lowest values
†Low amplitude QRS in leads 1, 2, and 3, left ventricular strain, inverted T waves in leads 1, 2 and 3, auricular fibrillation (7 cases), and auricular flutter (1 case)
(Kleckner *et al*, J A M A, April 23, 1955)

tract in patients with hemochromatosis, and that there is a greater uptake in these patients who are phlebotomized.[24 25 73 79 99] It has been found that needle biopsy of the liver, in particular, is the only reliable test available to diagnose hemochromatosis at the present time. If a finely granular cirrhosis and extensive deposits of iron are demonstrated histologically, the diagnosis of hemochromatosis is confirmed until disproved

Inasmuch as the presence of cirrhosis of the liver is a reliable distinction between hemosiderosis and hemochromatosis, it is worthwhile to point out a few of the characteristics of this variety of cirrhosis (Figs 2-5). The livers are generally larger than normal and are brown and finely granular (Fig 8). The granu-



FIG 6 Pancreas in hemochromatosis illustrating degeneration from fibrous connective tissue fatty infiltration and atrophy

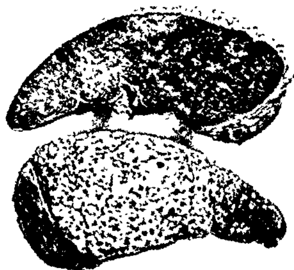


FIG 7 Spleen in hemochromatosis. Weight 468 gm Sagittal section and surface, hypertrophy chronic hyaline perisplenitis chronic passive congestion and marked fibrosis

larity is the result of the small closely spaced nodules of regeneration (Fig 9) These small nodules of regeneration and the narrow internodular zones of proliferated bile ducts and connective tissue are similar histologically to those observed in portal cirrhosis In addition to the extensive deposits of hemosiderin, the cirrhosis associated with classic hemochromatosis differs from

TABLE VI

LABORATORY DATA IN FORTY-TWO PATIENTS WITH HEMOCHROMATOSIS

Determination	Patients Tested, No	Results*
Hemoglobin, gm /100 cc	42	10 4 (17.2 2.5)
Erythrocytes, millions/cu mm	42	3 12 (5 04-0 87)
Leukocytes, per cu mm	42	8,125 (22,000 3,700)
Albuminuria	42	12
Erythrocyturia	42	2
Blood glucose, mg /100 cc	19	234 (476 98)
Blood urea, mg /100 cc	17	77 (178 28)
Serum bilirubin, mg /100 cc	20	
Direct		2 4 (11 3 0)
Indirect		1 9 (7 2-1.2)
Sedimentation rate (Westergren)	10	44 (77 22)
[illegible]	11	Grade 1 4
[illegible]	18	2 5 5 5 to 2 9 2 6
[illegible]	5	Low in 4
[illegible]	5	Low in 4
[illegible]	5	Macrocytosis
Prothrombin time, seconds (normal 17-19)	16	25 (20-23)
Cephalin cholesterol flocculation	7	Abnormal in 4
Thymol turbidity	8	Abnormal in 2
Biopsy		
Skin	10	Iron in 8
Liver	8	Diagnostic in 8
Estrogens in urine	1	Normal
Blood phospholipids, mg /100 cc	1	167
Blood lipids, mg /100 cc	1	255
Electrocardiogram	24	Abnormalities present in 22†
Electrophoresis of serum protein	4	Normal

*Numbers in parentheses are highest and lowest values

†Low amplitude QRS in leads 1, 2, and 3, left ventricular strain, inverted T waves in leads 1, 2 and 3, auricular fibrillation (7 cases), and auricular flutter (1 case)

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the typical portal variety in that, in about a fourth of the cases, it appears to be in an early stage of development. In our cases, there were many lobules present with central veins and a normal architectural pattern (Fig 10). In many cases of hemochromatosis, the regenerative nodules are elongated and bizarre in shape and are present in some cases in a garland-like pattern not unlike the appearance of posthepatitic cirrhosis (Fig 11).[124] In general, however, the large size of the liver, the small regenerative nodules and the absence of broad bands of atrophy do not suggest posthepatitic cirrhosis Further evidence that the cirrhosis is in an early stage of development is the fact that varices of the esophagus were present in only 20 per cent of all our cases, hypertrophy of the spleen (more than 250 gm) in only 40 per cent and ascites



Fig 8a Liver in hemochromatosis, colored reddish brown Weight 2,360 gm Uniform granular regenerative nodules (Courtesy, Kleckner, Baggenstoss, and Weir—Am J Clin Path – August, 1955)

Fig 8b Inferior surface of liver in hemochromatosis Same morphological features of Figure 8a

Fig 8c Sagittal section of Figure 8b



FIG. 9b. Needle biopsy of the liver from a patient with secondary hemochromatosis, who had aplastic anemia. Histologically although the cirrhosis is less advanced, there is no difference between the liver of the primary or classical type. (Prussian Blue X110).

FIG. 9c. Hepatoma in hemochromatosis. Needle biopsy of the liver. Note conspicuous absence of iron in malignant tissue. (H & E, X80)

in only 70 per cent The corresponding figures for alcoholic portal cirrhosis in 43 cases were 74, 83 and 88 per cent, respectively[6]

Although these histopathological distinctions hold for most of the cases of hemochromatosis, it must be conceded that the distribution of hemosiderin in transfusional hemosiderosis can occasionally mimic that seen in hemochromatosis, especially when many transfusions have been given over a prolonged period Pigment may occur even in the ductal epithelium of the liver, the pancreas, gastric glands, endocrine glands, and myocardium (Figs 6, 7, 12, 13, 14, 15) As Stewart has indicated, this observation may mean that the distribution of iron-containing pigment (and perhaps of other particular matter) *is not specific for any particular disease but rather that it may be related to the quantity present and the time during which it has been present*[120]

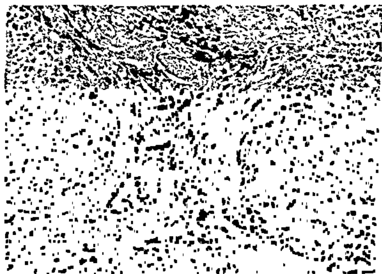


Fig. 9a Liver from a patient with classical or primary hemochromatosis *Histological features of cirrhosis, broadened stroma and deposits of iron (hemosiderin) in hepatic cells, Kupffer cells, stroma and bile ducts (Prussian Blue* X110)

Heredito-familial Type

Several reports have been made of hemochromatosis occurring in generations or in families.[1 22 33 43 60 68 79 81,107 115] The brother

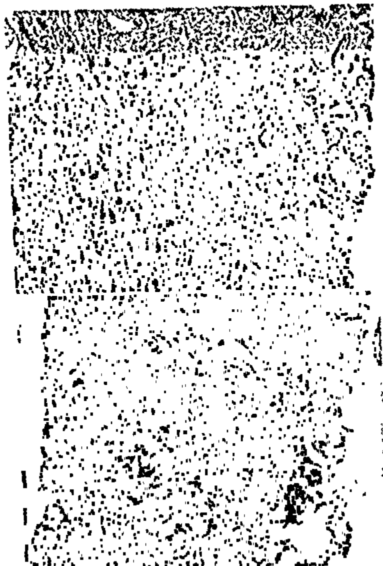


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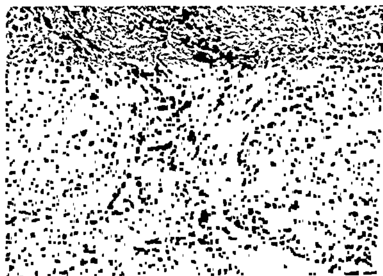


FIG 9a Liver from a patient with classical or primary hemochromatosis. Histological features of cirrhosis, broadened stroma and deposits of iron (hemosiderin) in hepatic cells, Kupffer cells, stroma and bile ducts (Prussian Blue X110)

Heredito-familial Type

Several reports have been made of hemochromatosis occurring in generations or in families.[1,22,33,43,60,68,79,81,105,113] The brother

in these cases resemble or are identical with those of primary hemochromatosis (Fig 16). Pigmentation of the skin and diabetes mellitus are clinical features in some cases. This condition has been reported in children and females, which is rare in primary hemochromatosis (Table VII).

TABLE VII

Clinical Findings in Seven Patients (Five Men and Two Women) with Hemochromatosis Associated with Chronic Refractory Anemia The Age at Death was 23 to 56 Years (Average 42 Years) and the Duration of Disease 2 to 11 Years (Average 5 Years)

Symptoms at Onset	*No of Cases*	*Eventual Symptoms*	*No of Cases*	*Physical Findings on Hospital Admission*	*No of Cases*
Weakness	3	Dyspnea	6	Pallor	7
Dyspnea	1	Weakness	5	Loss of weight	6
Purpura	1	Diabetes	1	Enlarged liver	6
Abdominal pain	1	Alcoholism	1	Pigmentation of skin	5
Weakness and dyspnea	1	Abdominal pain	1	Edema	5
		Gastrointestinal hemorrhage	1	Ascites	3
		Indigestion	1	Jaundice	2
				Enlarged heart	3
				Purpura	2
				Pleural effusion	2
				Spider angioma	1
				Loss of hair	1
				Testicular atrophy	1
				Erythrodontia	1

Types of Anemia	*No. of Cases*	*No of Blood Transfusions (0 5 liter)*	*No. of Cases*
Aplastic	4	25 50	2
Splenic	1	50 100	3
Hemolytic, acquired	1	100-150	1
Myelophthisic	1	250 300	1

Complications	*No of Cases*	*Causes of Death*	*No of Cases*
Reactions to transfusions	5	Congestive heart failure	4
Bronchopneumonia	2	Hepatic insufficiency	1
Hepatitis	1	Bronchopneumonia	1
Ileus	1	Pulmonary embolism	1
Varices (patent)	1		1

(Kleckner et al, J.A.M.A., April 23, 1955)

Table VIII shows the significant clinical data of 4 patients who had hemochromatosis associated with chronic anemia In these patients, the principal clinical features were weakness, dyspnea, edema, loss of weight and the pigmentation of the skin similar to that observed in primary hemochromatosis Diabetes mellitus occurred in only 2 of the 4 patients, all of whom were men The type of anemia was aplastic in 2 patients and macrocy-

of one of our patients died of hemochromatosis at 32 years of age. Two brothers with hemochromatosis 28 and 42 years of age, are *currently being treated with multiple phlebotomies* Their father had hemochromatosis and a half-sister has diabetes mellitus and an enlarged liver (Fig. 17).

SECONDARY HEMOCHROMATOSIS

Recent reports employ the terms "exogenous," "secondary" or "transfusional" hemochromatosis to distinguish from primary or classical hemochromatosis a type of hemochromatosis with chronic anemia, usually refractory in nature, in which treatment *has included oral or intravenous administration of iron* or use of multiple transfusions of blood.[1,4,10,27,28,46,53,55,66,70,71,72,79,80,84,86,87,92,97,108,111,113,116,118,130,133,140,141] The association of cirrhosis and anemia are the main clinical findings Histologically, the findings

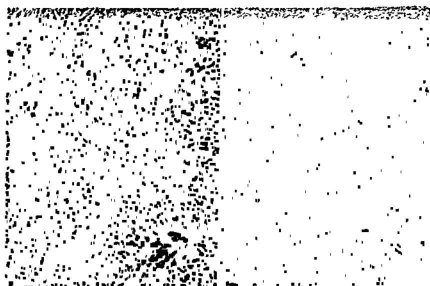


Fig 10 Liver in hemochromatosis, demonstrating an area in which normal vascular relationships persist. The portal tracts illustrate increased fibrous connective tissue, note stationary central vein (H & E, X35). (Courtesy, Kleckner, Baggenstoss, and Weir—Am J Clin Path—August, 1955)

Fig 11. Liver in hemochromatosis, histologically more advanced than in Figure 10 Note garland like regenerative nodules (H & E, X22). (Courtesy, Kleckner, Baggenstoss and Weir—Am J Clin Path—August, 1955)

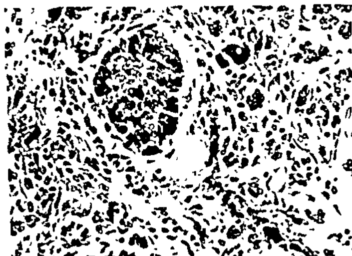


FIG. 12b Histological section from another case of hemochromatosis to demonstrate marked degeneration and atrophy of the acini and islets of Langerhans and increased fibrous connective tissue, fatty infiltration, round cell infiltration and deposits of iron in the glandular epithelium and stroma The patient had had diabetes mellitus (H & E, X300)

tic, hyperchromic in 2 patients (Table IX) The marrow was extremely active in one of the latter patients with a normoblastic erythropoiesis showing a pronounced shift to the left. All of these patients had received variable numbers of blood transfusions. Congestive heart failure was the cause of death in 2 and hepatic insufficiency in 1.

Pathologically, the lesions in these patients may differ only slightly from those in primary hemochromatosis Most striking are the hematological and bone-marrow changes resulting from disease of the hematopoietic system In addition, the cirrhosis appears to be in an early stage of development in these patients Many lobules persist in which a normal relationship is present between the central vein and portal tracts Regenerative nodules are present but are neither numerous nor fully developed The second patient in Table IX showed evidence of extensive degeneration and necrosis of hepatic cells in the centers of the remain-

TABLE VIII

SUMMARY OF CLINICAL DATA IN 4 PATIENTS WHO HAD HEMOCHROMATOSIS ASSOCIATED WITH CHRONIC REFRACTORY ANEMIA

	Patient			
	1	2	3	4
Clinical Diagnosis	*Aplastic anemia*	*Refractory anemia*	*Macrocytic hyper-chromic anemia*	*Macrocytic hyper-chromic anemia*
Age, onset	42	53	27	31
Age, death	47	56	31	living
Initial symptom	Dyspnea	Weakness	Weakness and dyspnea	weakness
Abdominal pain	+	–	–	–
Ascites	+	+	–	–
Edema	+	+	+	+
Jaundice	+	–	+	–
Weakness	+	+	+	+
Dyspnea	+	+	+	+
Pallor	+	+	+	+
Enlarged organs	–	liver, spleen	liver, heart	liver, spleen
Loss of weight	–	+	+	+
Pigmentation of skin	+	+	–	+
Number of blood transfusions (500 ml ea.)	58	125	10	8
Cause of death	Hepatic insufficiency	Congestive cardiac failure	Congestive cardiac failure	living

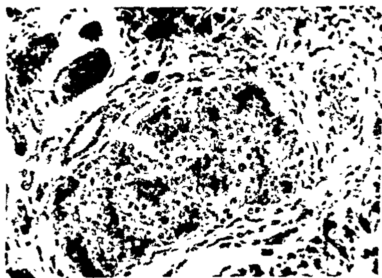


FIG. 12a Histological section of a pancreas with hemochromatosis from a patient who did not have diabetes mellitus, centrally there is a large, degenerative islet of Langerhans fibrosis, fatty infiltration and atrophy of acini, iron in islet of Langerhans, stroma, ducts, and acini (Prussian Blue, X300).

evidence of a causal relationship between the two.[40] Fibrosis and the duration of the disease did not correlate closely either It is known that anemia increases the amount of iron absorbed from the intestinal tract, but the relation of the anemia to the cirrhosis has not been clarified.[36] It has been suggested that the hypoxia induced by the anemia may be responsible for destruction of hepatic cells and subsequent cirrhosis. In discussing aplastic anemia, Zeltmacher and Bevans stated that they believed some toxin injured both the liver and bone marrow and that the increased absorption of iron occurred merely as a consequence of anemia, the iron having no local toxic effect [141] Inasmuch as patients with secondary hemochromatosis receive many transfusions, the possible role of viral hepatitis in the pathogenesis of the cirrhosis should be considered. Two patients with secondary hemochromatosis had had previous jaundice

Another contributing feature in many cases of secondary hemochromatosis is the fact that the amount of iron present in the tissues is greater than can be accounted for by the number of transfusions given It is apparent that these patients must have absorbed enough iron through the gastrointestinal tract to make up the difference. A single common denominator—anemia—is present in all the reported cases. It is apparent that many anemic patients continue to absorb iron whether they need it or not. Actual measurements utilizing radioactive isotopes have shown that some anemic patients continue to absorb appreciable quantities of iron If such a patient has had anemia continuously for a long period of time, it is theoretically possible for him to absorb large quantities of iron even without transfusions Alterations in the absorption of iron may also occur independently of anemia, as witnessed by the fact that absorption of iron can be greatly increased by diets in which corn is the principal source of protein While the amount of phosphorus in the diet influences the absorption of iron under these circumstances, other dietary factors also appear to be involved

HEMOSIDEROSIS

Hemosiderosis is defined as an excessive amount of iron stored in various tissues of the body. The quantity of iron usually does

TABLE IX
PERIODIC CLINICAL STUDY IN A CASE OF HEMOCHROMATOSIS WITH MACROCYTIC, HYPERCHROMIC ANEMIA

	Years			
Laboratory Tests	*1*	*2*	*6*	*6½*
HGB gm	9.3	17.2	5.3	18.2
RBC x 10^6	2.70	5.80	1.10	6.58
WBC	3,600	8,200	2,650	9,750
Platelets x 10^3	300	650	33	362 000
Retic. %	1.6	2.8	1.8	7
Hemat %	28	54	14	56
Sed rate mm /hr (Westergren)	63	5	111	10
BSP % 45 min	6	12	5	0
Glucose mg/100 cc	91	124	90	106
Albumin gm /100 cc	3.7		3.4	4.9
Globulin gm /100 cc	1.7	1.7	2.5	3.0
*Bilirubin mg /100 cc**	0.64	0.03	0.01	0.07
	2.06	0.32	0.89	0.39
Ceph Flocc	0	2+	3+	0
Thymol Turbidity	–	–	5	7.1
Prothrombin time	42%		92%	92%
Bone Marrow.	Megaloblastic		Megaloblastic	
Treatment	High protein, high carbohydrate, high caloric diet, liver extract, abdominal paracentesis Free HCL present in gastric juice	Treatment discontinued	same diet folic acid 5 mg t i d vitamins Brewer's Yeast Free HCL present in gastric juice	

ing lobules The parenchymal cells of the regenerative nodules contained less stainable iron than did the cells of the original persisting lobules. Atrophy and fibrosis of the pancreas, brown discoloration of the abdominal viscera and deposits of hemosiderin identical in amount and location to those demonstrated in primary hemochromatosis also were found.

Many workers have questioned whether the administration of large amounts of iron, either orally, intravenously or in the form of transfusions, produces hemochromatosis The content of iron in the tissues of a patient with chronic lymphatic leukemia who received 291 transfusions of 500 cc. of blood was as great as that observed in many cases of hemochromatosis and yet not even early cirrhosis of the liver had developed over a four-year period Ellis and associates found that siderosis and fibrosis generally paralleled one another in their cases, but could find no definitive

evidence of a causal relationship between the two.[10] Fibrosis and the duration of the disease did not correlate closely either. It is known that anemia increases the amount of iron absorbed from the intestinal tract, but the relation of the anemia to the cirrhosis has not been clarified.[24] It has been suggested that the hypoxia induced by the anemia may be responsible for destruction of hepatic cells and subsequent cirrhosis. In discussing aplastic anemia, Zeltmacher and Bevans stated that they believed some toxin injured both the liver and bone marrow and that the increased absorption of iron occurred merely as a consequence of anemia, the iron having no local toxic effect.[141] Inasmuch as patients with secondary hemochromatosis receive many transfusions, the possible role of viral hepatitis in the pathogenesis of the cirrhosis should be considered. Two patients with secondary hemochromatosis had had previous jaundice.

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HGB gm	9 3	17 2	5 3	18 2
RBC x 10^6	2 70	5 80	1 10	6 58
WBC	3,600	8,200	2,650	9,730
Platelets x 10^3	300	650	33	362,000
Retic %	1 6	2 8	1 8	7
Hemat %	28	54	14	56
Sed rate mm thr (Westergren)	65	5	111	10
BSP % 45 min	6	12	5	0
Glucose mg/100 cc	91	124	90	106
Albumin gm /100 cc	3 7		3 4	4 9
Globulin gm /100 cc	1.7	1 7	2 5	3 0
Bilirubin mg /100 cc.	0 64	0 03	0 04	0 07
	2 06	0 32	0 89	0 39
Ceph Flocc	0	2+	3+	0
Thymol Turbidity	—	—	5	7 1
Prothrombin time	42%		92%	92%
Bone Marrow.	Megaloblastic		Megaloblastic	
Treatment	High protein, high carbohydrate, high caloric diet, liver extract, abdominal paracentesis	Treatment discontinued	same diet folic acid 5 mg t i d. vitamins Brewer's Yeast	
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able iron Parenchymal cells throughout the lobule have extensive deposits of iron and especially large amounts are observed also in phagocytic cells Focal intralobular regeneration of hepatic cells may be detected and these cells contain smaller amounts of iron The normal lobular pattern is always intact in spite of tremendously widened portal spaces

One instance of transfusional siderosis with cirrhosis of the liver was found in an alcoholic patient who had a clinical and biopsy diagnosis of portal cirrhosis before transfusions were administered. No iron was observed in the material studied at biopsy. He received 54 pints of blood over a four month period before death. Sections of material obtained at necropsy revealed typical portal cirrhosis but iron was found in the Küpffer cells only In another case, Chalmers has written to me a report of a patient with hereditary telangiectasia who had repeated episodes of gastrointestinal hemorrhage Despite the administration of 300 transfusions of blood, no evidence of hemosiderosis was demonstrated at necropsy, suggesting that transfusional hemosiderosis does not occur in the presence of continued blood loss.

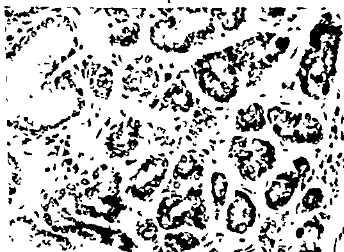


Fig 14a Stomach in hemochromatosis Iron is deposited particularly in epithelium of the chief cells and in interstitial tissue Postmortem autolysis (Prussian Blue, X300)

not equal that found in tissues in hemochromatosis, except when 200 or more transfusions of blood have been administered over a period of several years. A finely granular cirrhosis of the liver, the necessary criterion for the diagnosis of hemochromatosis (Figs 2, 3, 4) is not present and fibrosis of the pancreas, sexual hypoplasia, diabetes mellitus and pigmentation of the skin are found infrequently

In cases of transfusional hemosiderosis, the degree of deposition of iron in the liver varies greatly and poor correlation is noted between the amount of blood received and the degree of hemosiderosis In mild hemosiderosis, stainable iron appears to be largely in the Kuppffer cells, with small amounts in the hepatic cells at the periphery of the lobule In moderate degrees of hemosiderosis, most of the stainable iron also appears in the Kupffer cells, but these cells are frequently observed in clusters where disintegration of hepatic cells presumably occurs Stainable iron may be observed in practically all parenchymal cells, but amounts are greatest in the cells at the periphery of the lobule In severe hemosiderosis, the portal tracts are widened by connective tissue, increased numbers of bile ducts and phagocytes containing stain-



FIG 13. Heart in hemochromatosis Areas of fibrosis, atrophy, and deposits of iron occur in myocardial fibers (Prussian Blue, X300).

group has reported an unusual case of an eighty-five year old woman who had subsisted for years on tea and toast, and who eventually developed a refractory anemia, cirrhosis and extensive hemosiderosis of the liver, pancreas and periportal lymph nodes

TABLE X
AMOUNT OF IRON IN VARIOUS ORGANS IN HEMOCHROMATOSIS AND TRANSFUSIONAL HEMOSIDEROSIS

Case Number	*Organ*	*Weight, gm.*	*Mg of Iron per 100 gm Wet Tissue*	*Total Iron in Organ, gm*
Hemochromatosis				
5	Liver	2920	930	27 15
7	Liver	2648	1000	26 48
	Pancreas	—	340	—
11		1485	740	10 82
13	Liver	4800	420	20 16
	Pancreas	—	168	—
	Portal lymph node	—	2043	—
19	Liver	2150	643	13.82
	Heart	410	72	0.30
	Pancreas	100	287	0.29
	Portal lymph node	—	1460	—
	Stomach (segment)	—	41	—
21	Liver	2830	1670	47.30
	Heart	500	82	0 41
	Pancreas	300	413	1.24
	Portal lymph node	—	2702	—
	Stomach (segment)	—	27	—
24	Liver	1650	1867	30.80
	Heart	300	50	0 15
	Pancreas	110	325	0.36
	Portal lymph node	—	2189	—
	Stomach (segment)	—	33	—
25	Liver	1100	1342	14 76
	Heart	300	27	0 08
	Pancreas	80	291	0.24
	Portal lymph node	—	972	—
	Stomach (segment)	—	19	—
Transfusional hemosiderosis				
28	Liver	1950	101.5	1.98
30	Liver	650	8 1	0 05
	Pancreas	100	6 7	0 007
34	Liver	4550	416 0	18.90
	Pancreas	125	412 0	0.52
43	Liver	2600	185 0	4 81
	Heart	610	2 5	0 015
	Portal lymph node	—	257 4	—
	Stomach (segment)	—	0 8	—
45	Liver	1750	216 8	3 79
	Heart	350	3.2	0 011
	Pancreas	85	5.2	0 004
	Portal lymph node	—	522 0	—
	Stomach (segment)	—	1.2	—

(Kleckner, Baggenstoss, and Weir Am J Am Path Aug 1955)

The amount of iron contained in various organs at necropsy was determined chemically in cases of transfusional hemosiderosis and hemochromatosis According to Muirhead and his associates, the normal value for iron expressed as weight per 100 gm of wet tissue is 16.6 mg. for the liver and 7 37 mg for the pancreas[95] It is apparent that the livers of hemochromatosis contained from 25 to about 100 times the normal amount of iron Sheldon regarded 21 36 gm as the average total amount of iron in the liver of a patient with hemochromatosis.[115] The pancreas in the patients with hemochromatosis contained from 22 to 50 times the normal amount of iron, the heart contained from 10 to 80 times the normal amount of iron and the gastric tissue contained about 20 to 45 times the normal amount of iron (Table X). Quantities of iron equivalent to those demonstrated in hemochromatosis were found in only one of our patients with transfusional hemosiderosis. This patient had received 291 pints of blood over a three and one-half year period. It is apparent that enormous amounts of iron must be given and retained in order to have the tissues saturated with iron, as in hemochromatosis

These chemical determinations of iron, in the tissues indicate that in most cases the higher content of iron in hemochromatosis will distinguish it from transfusional hemosiderosis but that occasionally the amount of iron in hemosiderosis may be equal to that observed in hemochromatosis Again, it is apparent that the only unfailing distinction between these two entities is the presence of a finely granular cirrhosis in hemochromatosis

Malnutritional Type

Extensive hemosiderosis has been described in malnutrition Gillman and Gillman described a condition called "cytosiderosis" among the African Bantu tribe and Gore reported hemosiderosis associated with pellegra in malnourished South Africans[49,50 54 129] Higginson has studied malnutritional hemosiderosis and observed that diabetes mellitus is extremely rare, that cirrhosis is present in a fourth of cases of severe malnutrition and that the iron is found mainly in the reticuloendothelial system.[62 63] Wyatt has mentioned hemosiderosis in concentration-camp victims. His

group has reported an unusual case of an eighty-five year old woman who had subsisted for years on tea and toast, and who eventually developed a refractory anemia, cirrhosis and extensive hemosiderosis of the liver, pancreas and periportal lymph nodes

TABLE X

AMOUNT OF IRON IN VARIOUS ORGANS IN HEMOCHROMATOSIS AND TRANSFUSIONAL HEMOSIDEROSIS

Case Number	*Organ*	*Weight, gm*	*Mg of Iron per 100 gm Wet Tissue*	*Total Iron in Organ, gm*
Hemochromatosis				
5	Liver	2920	930	27.15
7	Liver	2648	1000	26.48
	Pancreas	—	340	—
11		1485	730	10.82
13	Liver	4800	420	20.16
	Pancreas	—	168	—
	Portal lymph node	—	2013	—
19	Liver	2150	643	13.82
	Heart	410	72	0.30
	Pancreas	100	287	0.29
	Portal lymph node	—	1460	—
	Stomach (segment)	—	44	—
21	Liver	2830	1670	47.30
	Heart	500	82	0.41
	Pancreas	300	413	1.24
	Portal lymph node	—	2702	—
	Stomach (segment)	—	27	—
24	Liver	1650	1867	30.80
	Heart	300	50	0.15
	Pancreas	110	325	0.36
	Portal lymph node	—	2189	—
	Stomach (segment)	—	35	—
25	Liver	1100	1312	14.76
	Heart	300	27	0.09
	Pancreas	80	294	0.24
	Portal lymph node	—	972	—
	Stomach (segment)	—	19	—
Transfusional hemosiderosis				
28	Liver	1950	101.5	1.98
30	Liver	650	8.1	0.05
	Pancreas	100	6.7	0.007
34	Liver	4530	416.0	18.90
	Pancreas	125	412.0	0.52
43	Liver	2600	185.0	4.81
	Heart	610	2.5	0.015
	Portal lymph node	—	257.4	—
	Stomach (segment)	—	0.8	—
45	Liver	1750	216.8	3.79
	Heart	350	3.2	0.011
	Pancreas	85	5.2	0.004
	Portal lymph node	—	522.0	—
	Stomach (segment)	—	1.2	—

(Kleckner, Baggenstoss and Weir, Am. J. Path., Aug. 1955.)

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11		1485	740	10.82
13	Liver	4800	420	20.16
	Pancreas	—	168	—
	Portal lymph node	—	2045	—
19	Liver	2150	645	13.82
	Heart	410	72	0.30
	Pancreas	100	297	0.29
	Portal lymph node	—	1160	—
	Stomach (segment)	—	41	—
21	Liver	2830	1670	47.30
	Heart	500	82	0.41
	Pancreas	300	413	1.24
	Portal lymph node	—	2702	—
	Stomach (segment)	—	27	—
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	Pancreas	85	[illegible]	[illegible]
	Portal lymph node	—	[illegible]	—
	Stomach (segment)	—	[illegible]	—

(Kleckner, Baggenstoss and Weir: Am. J. Clin. Path., Aug. 19[illegible])

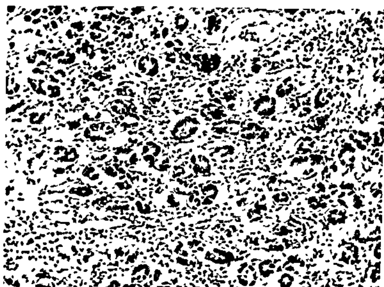


FIG 14b Stomach in severe hemosiderosis (Figure 3) Identical histological features to Figure 14a

[139] Malnutritional hemosiderosis as an entity has not been reported in America One of twenty patients with hemosiderosis and extensive chronic ulcerative colitis, which eventually required a total colectomy, had also a history of profound and prolonged malnutrition Cachexia, abnormalities in electrolytic and fluid balance, intractable diarrhea, hypoalbuminemia and fatty infiltration of the liver were present

Exogenous Type

Hemosiderosis produced by transfusions of blood and the oral or intravenous administration of iron is not uncommon, particularly among males [16,17,26,77-79,91-93,135,136-140] There is no conclusive evidence that exogenous hemosiderosis produced in humans or in experimental animals progresses to hemochromatosis

Associated with Various Refractory, Megaloblastic or Hemolytic Anemias

Hemosiderosis has been found in Cooley's anemia, sickle cell anemia, pernicious anemia and hemolytic anemia [40-44,77-78,80-93,109]



FIG. 15 Thyroid gland in hemochromatosis Iron in epithelium of colloid and interstitial tissue (Prussian Blue, X300)

[118,133,137] This type of hemosiderosis is an incidental histopathological finding in most instances

Does Hemosiderosis Progress to Hemochromatosis?

This question has been answered affirmatively and negatively and, as Dubin re-emphasizes, much of the difference of opinion lies in the clinical and pathological criteria employed in defining hemosiderosis, hemochromatosis, and cirrhosis.[45] On the basis of the studies of Baggenstoss, Weir, Kark, and this author, which, to date, consist at of 35 necropsy cases of primary hemochromatosis, 7 cases of secondary hemochromatosis and 21 cases of hemosiderosis (20 cases of transfusional hemosiderosis and 1 case of malnutritional hemosiderosis), and 9 living patients with primary hemochromatosis and 1 living patient with secondary hemochromatosis, it has been established that definite clinical and pathological criteria are mandatory in defining these conditions [74-79] An unpublished review of necropsy cases of hemosiderosis associated with various anemias, a common histopathological finding, did not offer any conclusive morphological evidence that

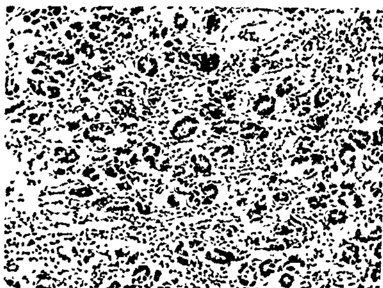


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hemosiderosis of this type was a transitional state of hemochromatosis Pathologically, a finely granular cirrhosis, pancreatic fibrosis, testicular atrophy and tremendous distribution of hemosiderin in the liver, heart, stomach, abdominal lymph nodes, and all of the endocrine glands define hemochromatosis Hepatosplenomegaly, physical stigmata of portal cirrhosis, diabetes mellitus, and cutaneous melanosis in males characterize clinical primary hemochromatosis Congestive heart failure, hepatic insufficiency, intercurrent infections, or hepatoma may herald the terminal clinical course of hemochromatosis In secondary hemochromatosis, the clinical and pathological characteristics are identical with the primary variety except for a refractory anemia of some type, usually aplastic anemia and alterations in the structure of the bone marrow Congestive heart failure is the most common cause of death On the other hand, hemosiderosis of any type is not a disease but a pathological condition in which hemosiderin usually is stored in the reticuloendothelial system. The amount of iron stored and its distribution in hemosiderosis, however, may resemble that deposited in the tissues in patients with hemochromatosis only, for example, after 200 or more transfusions of 500 cc of blood are administered (about 50 gm of iron)

The pathological definition of cirrhosis includes nodular intrahepatic regeneration, portavenous anastomoses, in particular, and fibrosis, and hepatic necrosis of the liver. Cirrhosis should not connote solely fibrosis of the liver If these strict pathological criteria of cirrhosis are applied to cases of primary or secondary hemochromatosis, most cases of "exogenous" or "transfusional" hemochromatosis would vanish, and the student of iron-storage diseases is now left to explain an important question· Do transfusions of blood or iron administered intravenously or orally over a prolonged period to patients with various types of chronic anemias produce secondary hemochromatosis?

The evidence that iron per se does not produce hemochromatosis is summarized briefly as follows: (1) The administration of iron, intravenously, orally, or in the form of transfusions of blood to humans produces transfusional hemosiderosis and not hemochromatosis. As many as 291 pints of blood (72.75 gm. of

iron) over a period of three and one-half years in one of our patients with chronic lymphatic leukemia, a refractory anemia, and without evidence of loss of blood, did not result in cirrhosis and pancreatic atrophy and fibrosis, invariable pathologic findings of hemochromatosis. This patient had extensive hemosiderosis and the iron in various tissues of the body was comparable to that found in hemochromatosis Moore reports a patient receiving 587 transfusions containing well over 100 gm of iron who had no evidence of hemochromatosis[81] Twenty cases of transfusional hemosiderosis were studied at necropsy and the usual clinical and pathological findings found in patients with hemochromatosis such as cirrhosis, testicular atrophy, and atrophy of



FIG. 16 Liver in secondary hemochromatosis from another patient with aplastic anemia. Note characteristic histological features of hemochromatosis Morphologically this is more advanced than in Figure 9b (H & E, X45) (Courtesy, Kleckner, Baggenstoss, and Weir—Am J Clin Path—August, 1955)

the pancreas were absent and the classic clinical features of hemochromatosis and extensive deposition and amounts of hemosiderin in the liver, pancreas, stomach, heart and endocrine glands were rare.

(2) The administration of iron to experimental animals, orally or parenterally in one form or another or in combination with cirrhotogenic diets over long periods of time produces hemosiderosis No convincing evidence to date has demonstrated that cirrhosis, a basic condition with respect to hemochromatosis, has been produced experimentally by prolonged administration of iron to experimental animals [17 20,21 31,43 92,91,94,95,101,102 103 108 123 136-139]

(3) The amount of iron administered to patients in the form of transfusions of blood therapeutically does not correlate with the degree of hepatic, myocardial, or pancreatic fibrosis, nor cirrhosis [12,14 62,63 77 91 136-139] One of our patients with hemochromatosis received 56 pints of whole blood, but estimation quantitatively of the amount of iron in the liver, heart, portal lymph node, and stomach far exceeded the amount administered exogenously.

(4) Radioisotopic iron absorption studies disclose an immediate increased uptake of radioiron in most patients with established hemochromatosis and more delayed, though lower uptake in patients with various types of anemias, especially hypochromic, microcyte anemia, pernicious anemia in relapse, hemolytic anemia, thalassemia minor, renal anemia and aplastic anemias.[36] Recent studies indicate that patients with hemochromatosis after many phlebotomies absorb considerably more iron through the intestinal tract than before phlebotomies It has been suggested that the "mucosal block" of iron in the duodenum is interrupted significantly in the early stages of hemochromatosis and again after a course of multiple phlebotomies in this disease [12 14 21 23 30-32 56-37 79 91 99]

(5) Increased deposits of lipofuscin, which a few observers believe is a histological characteristic of hemochromatosis, is not present in transfusional hemosiderosis.[14 16,17 38 62 63]

(6) The prolonged administration of iron in one form or another in humans does not lead to significant abnormalities in

the electrocardiogram, hepatic function tests, or glucose tolerance tests as are commonly observed in patients with hemochromatosis [12, 14, 61, 75-79, 119, 125]

(7) Treatment of patients with portal cirrhosis and anemia by transfusions of blood has not been proved to eventuate in hemochromatosis

(8) It has been demonstrated that members of the Bantu tribe ingest in their diet from 100 to 200 mg of iron daily As a result, nutritional hemosiderosis develops which does not produce fibrosis independently, and there is no satisfactory evidence that nutritional hemosiderosis per se results in hemochromatosis [45, 50, 62, 63]

(9) On the basis of clinical and necropsy evidence, there is no documented proof of an increased incidence of hemochromatosis in those areas of the United States where the content of iron in the soil is high such as the iron-mining districts Kashin-Beck's disease which occurs in Manchurians who ingest large quantities of iron, on the other hand, resembles hemochromatosis [64]

PROGNOSIS

At the present time, it is estimated that untreated patients with primary hemochromatosis survive from four to five years after the onset of clinical symptoms The duration of the disease has been known to range from a few months to twenty five years and over Sheldon found the average life expectancy in series to be about two years [115] Correct management of diabetes mellitus, hepatic dietotherapy and chemotherapeutic and antibiotic drugs have increased the survival rate Whereas the prognosis of patients with primary hemochromatosis treated by multiple venesections appears to be improved, more time is required to evaluate the prognosis of these patients treated by phlebotomy Nevertheless, phlebotomized patients with hemochromatosis still die from the usual causes of death

The duration of the secondary hemochromatosis is from two to eleven years Sheldon never mentioned this type in his monograph presumably because repeated transfusions of blood necessary to maintain the life of these patients, were not generally employed. On the other hand, Bomford and Rhoads' patient with

aplastic anemia survived thirty years, Ellis' case twenty-six years, and a patient from the Massachusetts General Hospital for twenty-five years [11,40,87]

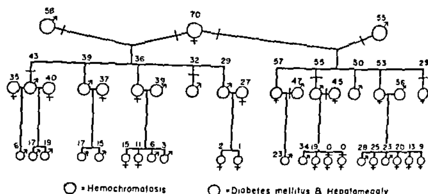


Fig 17 (Courtesy, Kleckner, M S, Jr, Kark, R. M, Baker, L A, Chapman, A Z, Kaplan, E, and Moore, T. J—J.A M A.—1955)

TREATMENT OF HEMOCHROMATOSIS

The supportive treatment of hemochromatosis consists of the conventional managements of cirrhosis and its complications, when present, congestive heart failure, cardiac arrhythmias, and diabetes mellitus When the rare complication of pancreatogenous steatorrhea is present, the amount of dietary fat should be reduced and U S P. pancreatin prescribed in doses of 10 to 15 gm. daily together with ample amount of fat-soluble vitamins

Balfour first recorded a technique of multiple massive phlebotomies as definitive treatment of hemochromatosis [6] This intriguing therapeutic technique was then popularized by Davis and Arrowsmith, and, eventually, by other investigators [80-82,66,67,69,85,96,132] In order to remove a sufficient amount of iron stored in the tissues in hemochromatosis, it is recommended that 500 cc. of blood be removed weekly Due to cirrhosis in this condition, it is recommended that the plasma be reinfused regardless of the inactivity of the cirrhosis. If the level of hemoglobin in the blood falls below 10 gm. 100 cc, weekly phlebotomy is delayed until

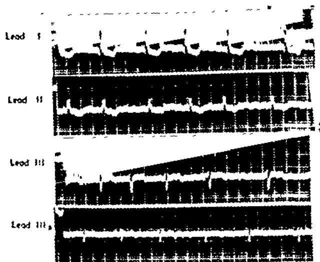


FIG 18 Electrocardiogram of a patient with hemochromatosis, congestive heart failure, auricular fibrillation, digitalis T waves.

the anemia is corrected It has been demonstrated that not only will iron-stores reaccumulate unless phlebotomies are continued indefinitely, but the absorption of iron is increased after phlebotomies This together with the discomfort to the patient are disadvantageous features of phlebotomy If therapeutic phlebotomies are continued in patients with primary hemochromatosis, clinical, biochemical and histopathological improvement has been demonstrated, the latter by diminution in the amount of iron in a hepatic biopsy Davis has shown that an "iron-free state" can be established in patients with primary hemochromatosis by multiple phlebotomies The oral administration of aluminum hydroxide in doses of 4 to 8 cc four times daily has been recommended to decrease absorption of iron by increasing the pH of the duodenal contents to maintain iron in the less readily absorbable ferric state.

The therapeutic results of phlebotomy in four patients with hemochromatosis is shown in Table XI and XII After one and one-half years objective results were less impressive than the re-

sults in most reported cases, because phlebotomy was not intensive (Fig 19) At the end of this period of time, the amount of phlebotomy in case 1 was 14,750 cc., in case 2, 12,500 cc., in case 3, 16,500 cc , and in case 4, 3,000 cc., after three years of this treatment At the conclusion of four and one-half years of treatment, these patients have maintained their health excepting case 4, who had tuberculosis, for which reason phlebotomy was discontinued (Fig 20). While the subjective and objective therapeutic results of phlebotomy in patients with primary hemochromatosis are impressive indeed, it must be remembered that the nutrition-

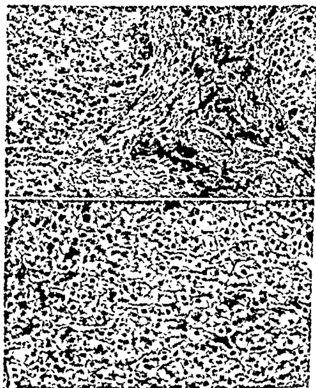


Fig 19a Specimen obtained by serial needle biopsy of the liver from a patient with hemochromatosis prior to treatment by massive, multiple phlebotomy Characteristic histological features (Prussian Blue, X110).

Fig. 19b Liver obtained by needle biopsy from the same patient eighteen months later following massive, multiple phlebotomy (case 2). Note unusual reduction in the amount of hemosiderin (Prussian Blue, X150).

TABLE XI
THERAPEUTIC RESULTS OF PHLEBOTOMY IN FOUR MEN WITH HEMOCHROMATOSIS

	Case 1	*Case 2*	*Case 3*	*Case 4*
Age	43	29	51	55
Treatment				
Diet	2,650 cal	Ad libitum	2,600 cal	2,100 cal
Isophane insulin (NPH)	70 units	None	20 units	30 units
Amount of phlebotomy				
After Three and One Half Years of Therapy				
Subjective status	Improved	Improved	Improved	Tuberculosis
Physical findings	Unchanged	Improved	Unchanged	Unchanged
Isophane insulin	40 units	None	None	40 units
Liver biopsy	Unchanged	70% less iron	Unchanged	Unchanged
Liver profile	Improved	Unchanged	Improved	Unchanged
Serum iron	Increased	Decreased	Increased	Increased
Iron bound globulin	Unchanged		Increased	Unchanged
Electrocardiogram	Unchanged	Unchanged		Abnormal

(Kleckner et al., J.A.M.A., April 23, 1955.)

TABLE XII
THERAPEUTIC RESULTS OF PHLEBOTOMY IN FOUR MEN WITH HEMOCHROMATOSIS*

	Case 1	*Case 2*	*Case 3*	*Case 4*
Age	46	52	57	58
Treatment				
Diet	3,200 cal	Ad libitum	2,600 cal	2,100 cal
Isophane insulin (NPH)	34 units	none	30 units	80 units
Amount of phlebotomy	31,750 cc	25,000 cc	33,500 cc	7,500 cc
After Five Years of Therapy				
Subjective status	Improved	Unchanged	Unchanged	Worse
Physical status	Improved	Unchanged	Worse	Worse
Liver biopsy	Unchanged	Unchanged	Less iron	More iron
Liver profile	Unchanged	Unchanged	Unchanged	Unimproved
Serum iron	Decreased	Unchanged	Unchanged	Unchanged
Iron bound globulin	Decreased	Unchanged	Unchanged	Unchanged
Electrocardiogram	Unchanged	Unchanged	Unchanged	Unchanged

*Courtesy, Dr. Ervan Kaplan

al, diabetic and hygienic status of these patients also have been treated and in two instances the abuse of alcohol restricted. Six patients with primary hemochromatosis have been observed periodically over a period as long as seven years. Treatment has consisted of the conventional management of cirrhosis, diabetes mellitus, and cardiac arrythmias without multiple phlebotomy. The therapeutic results of this group are just as impressive as the

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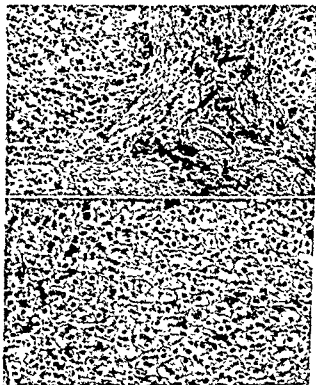


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THERAPEUTIC RESULTS OF PHLEBOTOMY IN FOUR MEN WITH HEMOCHROMATOSIS

	Case 1	Case 2	Case 3	Case 4
Age	45	29	51	55
Treatment				
Diet	2,650 cal	Ad libitum	2,600 cal	2,100 cal
Isophane insulin (NPH)	70 units	None	20 units	50 units
Amount of phlebotomy				
After Three and One Half Years of Therapy				
Subjective status	Improved	Improved	Improved	Tuberculous
Physical findings	Unchanged	Improved	Unchanged	Unchanged
Isophane insulin	40 units	None	None	40 units
Liver biopsy	Unchanged	70% less iron	Unchanged	Unchanged
Liver profile	Improved	Unchanged	Improved	Unchanged
Serum iron	Increased	Decreased	Increased	Increased
Iron bound globulin	Unchanged		Increased	Unchanged
Electrocardiogram	Unchanged	Unchanged		Abnormal

(Kleckner et al., J.A.M.A., April 23, 1955)

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THERAPEUTIC RESULTS OF PHLEBOTOMY IN FOUR MEN WITH HEMOCHROMATOSIS*

	Case 1	Case 2	Case 3	Case 4
Age	46	35	57	[illegible]
Treatment				
Diet	3,200 cal	Ad libitum	2,600 cal	2,100 cal
Isophane insulin (NPH)	31 units	none	30 units	60 units
Amount of phlebotomy	31,750 cc.	25,000 cc	33,300 cc	7,500 cc
After Five Years of Therapy				
Subjective status	Improved	Unchanged	Unchanged	Worse
Physical status	Improved	Unchanged	Worse	Worse
Liver biopsy	Unchanged	Unchanged	Less iron	More iron
Liver profile	Unchanged	Unchanged	Unchanged	Unimproved
Serum iron	Decreased	Unchanged	Unchanged	Unchanged
Iron bound globulin	Decreased	Unchanged	Unchanged	Unchanged
Electrocardiogram	Unchanged	Unchanged	Unchanged	Unchanged

*Courtesy, Dr. Ervan Kaplan

al, diabetic and hygienic status of these patients also have been treated and in two instances the abuse of alcohol restricted. Six patients with primary hemochromatosis have been observed periodically over a period as long as seven years. Treatment has consisted of the conventional management of cirrhosis, diabetes mellitus, and cardiac arrythmias without multiple phlebotomy. The therapeutic results of this group are just as impressive as the



phlebotomized patients.[75] Therapeutic phlebotomy as a specific treatment of patients with primary hemochromatosis must be evaluated properly only after these conventional therapeutic measures are controlled adequately.

Edathamilcalciumdisodium (calcium disodium Versenate), the calcium chelate of ethylenediaminetetraacetic acid has been administered intravenously to patients with hemochromatosis. This substance forms a nonionic, water-soluble compound with heavy metallic ions, producing an excretion of urinary iron. The amount of iron mobilized is too small to be practical.[75,79,124] Improved chelating agents such as Versonol (N-hydroxyethyl-ethylenediamine triacetic acid) and penicillamine have been investigated.[14,45,83,114] While they appear to more effectively bind stored iron, they have distinct disadvantages of being an intravenous preparation. At the present time, neither a satisfactory nor practical chelating agent is known.

The treatment of secondary hemochromatosis is no different than the primary type with the exception of phlebotomy. In contradistinction, the administration of multiple transfusions of blood prolongs the life of the patient. It is apparent that the reduction of iron stores in these patients must be accomplished by the use of some chelating agent. Finch and Barnett, on the other hand, successfully treated a patient with hemochromatosis and moderate anemia and neutropenia by phlebotomies.[42] Hemochromatosis with megaloblastic anemia has been reported to respond to the administration of folic acid.[55,75]

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FIG. 20a. Liver obtained by needle from another patient with hemochromatosis prior to treatment by massive, multiple phlebotomy (case 8). (Prussian Blue, X300)

FIG. 20b. Liver obtained by needle biopsy of the liver from the same patient four and half years following massive multiple phlebotomy. Note significant reduction in the amount of hemosiderin. (Prussian Blue, X300)



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Chapter 11

HEPATOLENTICULAR DEGENERATION (Wilson's Disease)

INTRODUCTION

HEPATOLENTICULAR DEGENERATION is a rare, frequently familial and progressively fatal condition usually observed in adolescents and young adults It is considered a metabolic defect of copper and amino-acid metabolism and maybe characterized by neurological abnormalities reflective of diseased extrapyramidal motor system and basal ganglia, mental deterioration and cirrhosis

In 1888, Gowers reported the first case of this condition as tetanoid chorea" in a boy and eventually in his sister[47,48] Westphal in 1883 and Strumpell in 1898 described in the German literature "pseudosclerosis" in which the neurological features of hepatolenticular degeneration are prominent[70,53,86,97] Omerod and Homen in 1890 and Anton of Halle in 1908 reported the association of cirrhosis with "obscure and fatal nervous symptoms"[6] It remained for S A K. Wilson in 1912 to document his classic monograph, *Progressive Lenticular Degeneration A Familial Nervous Disease Associated with Cirrhosis of the Liver.*[95] He described the neurological features of this condition as a syndrome of the corpus striatum," manifested by extrapyramidal motor signs as generalized tremor, involuntary muscular movements, dysarthria, dysphagia, muscular rigidity and hypertonicity, spasmodic contractions, contractures and progressive emaciation Dementia, inappropriate behavior, emotionalism and frank psychosis may be present The course of the disease was acute or chronic but progressively fatal Pathologically, bilateral symmetrical degeneration and atrophy of the putamen and globus pallidus were noted Postnecrotic cirrhosis was observed at necropsy but was considered asymptomatic during life A study of Wilson's original cases, however, discloses antecedent jaundice in three cases, terminal esophageal hemorrhage in one case and ascites

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Since Wilson's report, at least 200 cases of this disease have been mentioned in the literature Little has been added to Wilson's masterful clinicopathological description of hepatolenticular degeneration The disease has become more commonly recognized Several cases are recorded in most every large general hospital or mental institution Recently, the genetic trait, the metabolism of copper and aminoacids, and treatment with various chelating agents to increase excretion of urinary copper in this condition have been studied

ETIOLOGY AND PATHOGENESIS

There has been much speculative information concerning the etiology and pathogenesis of hepatolenticular degeneration. That the nervous and mental features of this disease are the result of hepatic injury has been a prevalent theory, particularly because

neuropsychiatric complications from several types of hepatitis, cirrhosis, hemochromatosis and metastatic hepatic disease have been observed[5 7 8 87 94] However, these conditions usually do not show the typical neurological disorder noted in hepatolenticular degeneration Interestingly, the concurrence of hemochromatosis and hepatolenticular degeneration has been reported[7 21 93] Hepatic injury and neurological symptoms similar to those of hepatolenticular degeneration have been produced experimentally by injections of manganese chloride[40 45] Kernicterus, the cerebral complication of erythroblastosis fetalis, has a striking similarity to hepatolenticular degeneration because of localized lesions in the basal ganglia and abnormal hepatic function The association of cirrhosis of the liver and nervous symptoms in domestic animals in various parts of the world has been noted, and in some instances lesions similar to hepatolenticular degeneration have been found Wilson's theory that an endogenous toxin was responsible for hepatolenticular degeneration has never been substantiated

Two etiological factors, namely a heredofamilial trait and a metabolic disturbance in the metabolism of copper and amino acids have been considered to explain the pathogenesis of hepatolenticular degeneration

It has been established that the liver, kidneys, basal ganglia, and corneal rings, in particular, of patients with this disease contain a marked increase in the amount of stored copper[4 10 24 26 33 35-37 50 63 71 72 79] However, that the deposition of copper produces the pathological lesions of hepatolenticular degeneration has not been proven Needle biopsy of the liver obtained from patients with hepatolenticular degeneration and stained with rubeanic acid reveals stainable copper[28 65 92]

In patients with hepatolenticular degeneration, the amount of total serum copper is decreased or normal, the concentration of ceruloplasmin, a specific alpha$_2$ globulin to which the greater part of the serum copper is normally bound, is decreased, the direct-reacting fraction of copper, which is probably bound to albumin, is increased, the urinary excretion of copper is increased, and there is increased absorption of copper from the gastrointestinal tract[4 12-15 25 26 35-37 39 52-55 78-81 91 101,105] Despite hy-

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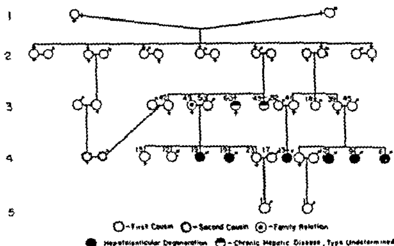


Fig. 1 Pedigree of a family with hepatolenticular degeneration

to serum albumin is not utilized in the synthesis of ceruloplasmin, but excreted in the urine or disposited in various organs where the affinity for copper is greater than serum albumin. This concept then regards cirrhosis, renal tubular and cerebral lesions as the result of copper intoxication.

GENETIC ASPECTS

Wilson, who originally reported a familial history in 8 of his 13 cases, remarked that the condition "was often familial but not congenital or hereditary."[95] Exposure of several members of a family to an identical environment and common inheritance has been postulated to explain the familial character of the disease. Others have thought that the disease is inherited in a recessive manner.[85] Bearn, who studied 26 cases of hepatolenticular degeneration in 16 families, found a cousin consanguinity rate in 37.5 per cent of the cases.[10] Examination of the pedigrees suggested to him that the disease is inherited in autosomal recessive manner. The total consanguinity rate of his cases was 62.5 per cent. In 3 of the 9 cases in the present series (cases 2, 3, 8), there was a family history of hepatolenticular degeneration

percupruria these patients still retain a positive copper balance. Scheinberg and Gitlin initially demonstrated that one of the specific metabolic defects in hepatolenticular degeneration is failure of synthesis or deficiency of ceruloplasmin.[80] Deficiency of ceruloplasmin in this condition has been confirmed by other investigators.[3,10,12,13,20,67] The amount of ceruloplasmin is proportionate to the amount of indirect-reacting serum plasma and also the oxidase activity of serum.[62] Recently, a relatively new and simple test has been devised to measure serum oxidase activity (ceruloplasmin).[76] Uzman and his associates in 1948 disclosed that the liver in patients with hepatolenticular degeneration contains an abnormal protein fraction with an increased affinity for copper, suggesting that the excessive deposition of copper is not the primary pathogenetic factor but secondary to an abnormality in the metabolism of protein.[89]

Uzman and Denny-Brown described an abnormal amino aciduria, unrelated to the severity of the cirrhosis or amount of proteins ingested daily, in patients with hepatolenticular degeneration.[90-92] They found that amino aciduria was unaccompanied by significant elevation of plasma alpha-amino nitrogen level, and that there was no specificity in the pattern of urinary amino acids.[29,38,61,84] Increased excretion of dicarboxylic amino acid peptides and uric acid have been demonstrated in patients with hepatolenticular degeneration.[18,60] It has been suggested that the peptiduria in this condition results from the specific abnormal metabolism of protein and that these abnormal peptides block tubular reabsorption of amino acids and uric acid.[89,91] Others attribuate amino-aciduria, renal tubular defect, and even the cirrhosis to the basic disturbance in metabolism of copper.[4,14,29,61]

Consequently, two hypotheses on the pathogenesis of hepatolenticular degeneration have been postulated: (1) in one, the primary genetic defect is the excessive storage of and affinity for copper by certain proteins in the liver, brain, kidneys, and other tissues resulting in decreased ceruloplasmin, aminoaciduria, and peptiduria; (2) in the other, the primary effect of the abnormal gene, when present in homozygous form, is to diminish the normal synthesis of serum ceruloplasmin, and as a result, copper attached



Fig 2a and 2b Reproduced sagittal section of longitudinal and cross sections of a gross brain from a case of hepatolenticular degeneration Deeper pigmented bilateral symmetrical degeneration and atrophy of the putamen of the lenticular nucleus, in particular, a subcortical mass of the corpus striatum (Courtesy, Raskin and MacKenzie—Ment & Nerv Dis—Sept-Oct, 1954)

An unusually interesting pedigree was classified by Wirth and the author in which cousin marriages in one family were high and total consanguinity rate was even much higher (Fig. 1).

PATHOLOGICAL FEATURES

The classical pathological picture of the brain of patients having hepatolenticular degeneration is bilateral symmetrical degenetration, cystic cavitation, or atrophy of the putamen, globus pallidus, caudate nucleus, internal and external capsule, cerebral cortex and dentate nucleus in order of maximum involvement The neurons in these regions degenerate and atrophy giving way to glial proliferation (Fig. 2a, 2b) Cumings assayed quantities of copper varying from 39 4 to 156 5 mg. 100 gm of dry tissue in the liver in hepatolenticular degeneration compared with a normal range of 3 7 to 17 2 mg in various other types of hepatic disease [33] In the basal ganglia of patients with hepatolenticular degeneration, the values were 69 5 to 71.6 mg compared with a normal value of 6.1 to 12 0 mg /100 gm. Cartwright and others found the concentration of copper to be highest in the liver, followed, in order, by the white matter of the cerebellum, the gray matter of the cerebellum, the brain stem, the gray matter of the cortex, the basal ganglion, the white matter of the cortex, the spinal cord and the kidney. The remaining visceral organs and skeletal muscle had slightly elevated tissue copper.[26 27]

In hepatolenticular degeneration, the liver may have the gross pathological appearance of the nodular variety of postnecrotic cirrhosis (Figs 3a, 3b). The liver, on the other hand, may appear normal in rare instances. The size of the liver in this condition may be normal, atrophic or hypertrophic. The regenerative nodules, contrasted to those of portal cirrhosis, are larger than 1 cm in diameter and are less uniform in size The cirrhotic liver is not discolored as in hemochromatosis Histologically, at necropsy this cirrhosis discloses irregularly sized nodular regeneration, fibrosis, reduplication of bile ducts, infiltration of lymphocytes in the nodules and stroma, and depending upon the activity of the cirrhosis, necrosis of the hepatic cells (Fig 4a). Needle biopsy of the liver performed in patients with this condition may exhibit fatty infiltration, inflammatory cellular infiltration, portal fibro-

rinsing the needle in disodium versenate and distilled water in order to reduce contamination of the needle with copper

CLINICAL FEATURES

Hepatolenticular degeneration usually occurs in adolescents and very young adults. In fact, when the presence of cirrhosis is found in a child, hepatolenticular degeneration should be suspected. One of the youngest patients reported with this condition was five years old (Table I).[25] The youngest of 9 patients in the present series at the time of the initial symptom was twelve years old and the oldest 22 The disease has been observed only in Caucasians

There are several clinical variants of hepatolenticular degeneration The symptoms either may be predominantly hepatic, lenticular, a combination of the two, or the patient may be asymptomatic and have histobiochemical evidence of the disease The hepatic type or so-called "abdominal" Wilson's disease is the least common variety. It is usually found in children and

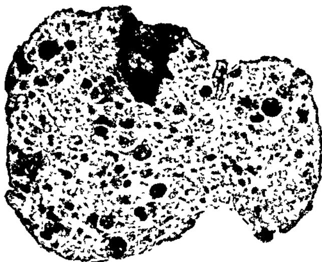


Fig 3b Sagittal section of same liver Note broad bands of stroma and irregularly enlarged regenerative nodules (Courtesy, *Alpers, B J*)

sis, or normal features. Normal hepatic architecture was found in a needle specimen in case 5. An important diagnostic procedure in patients with hepatolenticular degeneration has been the qualitative determination of copper in a specimen of liver obtained by needle biopsy (Fig. 4b) [28,58,92] Hepatic tissue is fixed in freshly prepared 0 1 per cent solution of rubeanic acid (dithiooxamide) in 70 per cent alcohol Ten to fifteen minutes later crystals of sodium acetate are added to make a 0 2 per cent solution Twenty-four hours later, the tissue is washed in 70 per cent alcohol twice in one hour and mounted in paraffin. Thick sections (10 to 15 microns) are then mounted on slides and studied without counterstaining or counterstaining with 0 1 per cent alcoholic cresyl violet. Black-stained copper is observed histologically in the hepatic cell Uzman and Chalmers consider this test an extremely valuable diagnostic measure. They recommend



FIG 3a Superior aspect of a liver from a case of hepatolenticular degeneration which is grossly morphological, a postnecrotic cirrhosis, weight 1,140 gm (case 9) (Courtesy, Alpers, B J)

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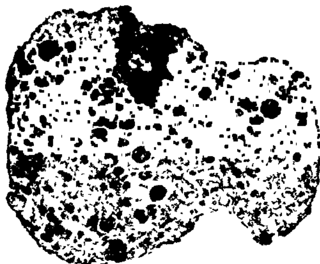


FIG. 3b. Sagittal section of same liver. Note broad bands of stroma and irregularly enlarged regenerative nodules. (Courtesy, Alpers, B. J.)

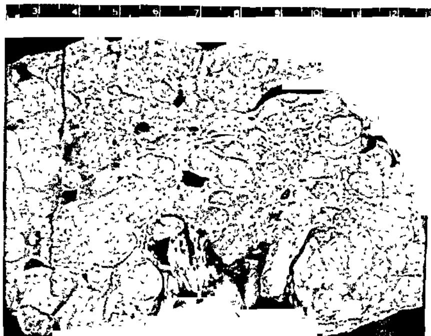
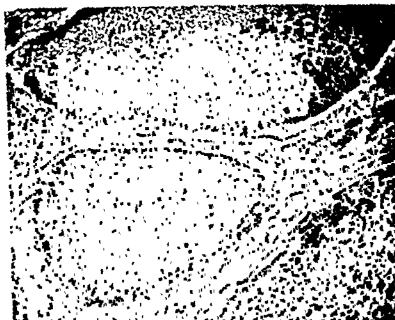


FIG 3c Sagittal section of another liver from a case of hepatolenticular degeneration, demonstrating distorted portovenous vessels and the structural features of postnecrotic cirrhosis (Courtesy, Raskin and MacKenzie—J Ment & Nerv. Dis—Sept Oct, 1954)

young adults and is characterized by features of cirrhosis such as hepatosplenomegaly, ascites, edema, spider angioma, palmar erythema, clubbing of fingers, bleeding tendencies and certain manifestations of portal hypertension, esophageal varices, collateral venous patterns and hypersplenism.[4,19,20,28,51,55,57] In many instances these patients die from cirrhosis either before development of nervous or corneal manifestations of hepatolenticular degeneration or these features may even develop terminally In both cases, the condition may go undiagnosed unless a family history of hepatolenticular degeneration is uncovered[8,28,36,45,59,69] Hepatolenticular degeneration has been reported in a patient with Cruveilhier-Baumgarten syndrome.[102]

Wilson's description of the lenticular and hepatolenticular types of this disease has not been improved upon. His classic



...nticular degeneration ... large regenerative nodules, dense ... necrosis Note distorted and displaced blood vessels (H & E, X80)

monograph should be perused by every student of hepatic diseases Cirrhosis may be absent, latent or asymptomatic in these types, but, invariably, is confirmed pathologically This type of the disease may have cyclic remissions but eventually progresses to mental deterioration, muscular deformity, dyskinetic phenomenon, and death The initial features can be dysphagia dysdiadochokinesia, tremors or weakness of an extremity A spontaneous regular alternating tremor at rest, choreotic, athetotic, or dystonic movements of the extremities or trunk, passive muscular rigidity and slow active movements are the significant dyskinetic features There is progressive deterioration in handwriting (Figs 5a, 5b) Drawn-in lips, fixed grin, vacuous laughing expression, inarticulate, monotonous speech, and excessive salivation characterize

further deterioration (Fig. 6). Dysphagia may contribute to malnutrition, generalized weakness and loss of weight. Lack of coordination and a regular or spontaneous alternating tremor characterize the well recognized "wing beating" or "Flugenschlagen." The Kayser-Fleischer ring, which consists of a brownish-green pigmentation of Descemet's membrane at the limbus of the cornea, pathognomonic of hepatolenticular degeneration, is observed less consistently in the hepatic than in the lenticular or



Fig 4b Needle biopsy of the liver from a patient with hepatolenticular degeneration The deeply stained particles are copper (Rubeanic acid, X450) (Courtesy, Chalmers, T C, Iber, F L, and Uzman, L L—New England J Med—1957)

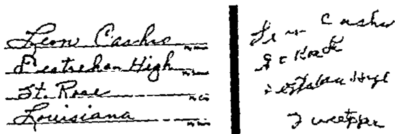


FIG 5a Comparison of the legibility of handwriting at one time *(left)* and nine years later *(right)* written by a patient with hepatolenticular degeneration demonstrating subsequent impaired penmanship (Courtesy, Schechter and Jones—Arch Int Med—1953)

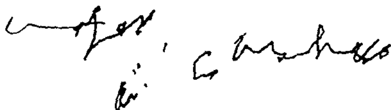


FIG 5b Progressive handwriting defect six more years due to myesthenia, intentional manual tremor muscular rigidity, joint and extremity contractures and dementia

hepatolenticular type (Figs 7a, 7b).[41,56] In the last two types, the ring is present almost without exception and may be associated with "sunflower cataracts" Rigidity, as in patients with paralysis agitans, is a common neurologic sign The patient eventually may have a stiff, jerky gait Inevitably, the concurrence of tremors, muscular rigidity, and emotional and mental deterioration results in inability satisfactorily to perform necessary daily habits and in falling spells; eventually, the patient becomes bedridden (Fig 8). A normal or superior intellectual status often gives way to progressive, belated mental deterioration, emotional outbursts of rage, laughter or crying, and abnormal behavior Some patients have been regarded initially as hysterical or psychotic, requiring psychiatric institutionalization Matthews thought that because of the invariably normal deep reflexes,

further deterioration (Fig. 6). Dysphagia may contribute to malnutrition, generalized weakness and loss of weight. Lack of coordination and a regular or spontaneous alternating tremor characterize the well recognized "wing beating" or "Flugenschlagen." The Kayser-Fleischer ring, which consists of a brownish-green pigmentation of Descemet's membrane at the limbus of the cornea, pathognomonic of hepatolenticular degeneration, is observed less consistently in the hepatic than in the lenticular or



Fig 4b Needle biopsy of the liver from a patient with hepatolenticular degeneration The deeply stained particles are copper (Rubeanic acid, X450) (Courtesy, Chalmers, T. C., Iber, F L., and Uzman, L L—New England J Med—1957)

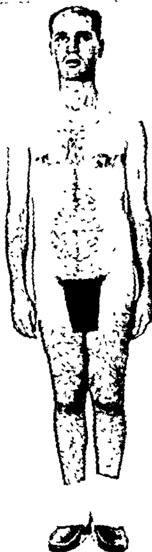


Fig. 6b Same patient. Weakness, generalized muscular rigidity, slight hepatomegaly, muscular atrophy, dysarthria, malnutrition, vegetativeness; photograph was made at 1/2 000 second in order to eliminate bodily rhythmic tremor. The patient had been treated beforehand with several courses of chelating agents including BAL, intensive physiotherapeutic measures, psychopharmacologic drugs and a nutritious diet prepared for chronic hepatic diseases.

sensation, vibration and lack of paralysis in these cases, the symptoms of hepatolenticular degeneration may be interpreted as functional, requiring penal incarceration A distinctive blue discoloration of the nails of the hands, azure lunulae, has been observed in hepatolenticular degeneration.[10]



Fig 6a Face of a patient with advanced hepatolenticular degeneration with spastic grin, fixed, childish expression, rigidity of facial muscles, drooling of saliva, dysarthria, and a pulsating spider angioma on the forehead

The clinical course of hepatolenticular degeneration may be acute with demise in several months, or it may be chronic with slowly progressive cerebral deterioration over a period of two or more decades. The acute attack (cases 1 and 9) is characterized by a febrile course with mental deterioration and extrapyramidal motor signs Although occurring chiefly in adolescents, it usually has predominant hepatic manifestations, such as hypersplenism, palpably enlarged liver, esophageal hemorrhage, edema and ascites. On the other hand, the more common chronic course is usually characterized by progressive dyskinetic neurological signs

TABLE I

CLINICAL DATA OF NINE CASES OF HEPATOLENTICULAR DEGENERATION

Case	Age	Sex	Initial Manifestation	Duration Symptoms (yr)	Bleeding Tendency	G-I Hemorrhage	Wgt Loss	Enlarged Liver	Enlarged Spleen	Edema	Ascites	Spider Angioma	Tremor	Athetosis	Dyssynergia	Mask like Facies	Mental Deterioration	Flexion Deformity
1	13	F	Fever	1	+	0	+	4+	3+	0	0	0	+	+	+	+	+	+
2	23	F	Athetosis	1	0	+	+	2+	1+	+	+	+	+	+	+	+	+	+
3	18	M	Dementia	½	0	0	+	1+	0	0	0	0	+	+	+	+	+	0
4	23	M	Dysphagia	2	0	0	+	0	1+	0	0	0	+	+	+	+	+	+
5	32	F	Paralyzed leg	12	0	0	+	0	0	0	0	0	+	+	+	+	+	+
6	18	F	Athetosis	3/12	0	0	0	0	0	0	0	0	+	+	+	+	0	+
7	27	M	Tremor	7½	0	0	+	0	0	0	0	+	+	+	+	+	+	+
8	19	M	Dysphagia	6/12	0	0	+	0	2+	+	+	0	+	+	+	+	+	+
9	17	M	Edema	2½	0	+	+	+	+	+	+	0	0	0	+	0	+	+

and mental deterioration with eventual or terminal hepatic disease

Another clinical variety type of hepatolenticular degeneration is asymptomatic, may or may not have histological evidence of cirrhosis, may be found in relatives of patients with established hepatolenticular degeneration, but have the biochemical features of the disease. Necropsy may disclose cirrhosis or neurological evidence of the disease

Hepatolenticular degeneration should be considered in any patient with indeterminate hepatomegaly, in any cirrhotic in whom the usual pathogenetic factor is not suspected, or in any patient with so-called "congenital" or "familial" cirrhosis The presence of Kayser-Fleischer rings will be found in over 90 per cent of patients and are a pathognomonic feature of the disease The most practical diagnostic methods are hyperuricuria and needle biopsy of the liver fixed and stained with rubeanic acid in alcohol The determinations of urinary amino acids and copper are usually difficult technical procedures

LABORATORY FINDINGS

Most patients with hepatolenticular degeneration have histological evidence of cirrhosis This is true in 8 of 9 patients in the current series (Tables I, II). In these patients, the bromsulfalein retention test yielded the most consistently abnormal results of the standard hepatic function tests. In case 6 in which the result of liver biopsy was normal, results of hepatic function tests were also normal except for a 6 per cent retention of bromosulfalein at 45 minutes The cirrhosis of hepatolenticular degeneration appears to be similar to that of hemochromatosis in which results of hepatic function tests may be normal in initial stages of the disease. Results of liver function tests are more apt to be abnormal in the hepatic or "abdominal Wilson" type or hepatolenticular degeneration. Jaundice and hyperbilirubinemia are usually observed only in the terminal stage of the disease Patients with the lenticular type of the disease, on the other hand, have a normal hepatic function except for minimal retention of bromsulfalein. There does not appear to be any difference in the comparative sensitivity of the cephalin-cholesterol flocculation, thymol tur-

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bidity, and zinc sulfate turbidity tests. Determinations of the serum albumin and globulin or electrophoretic patterns of serum protein were normal in 7 cases of the present series In Cooper's 7 cases of hepatolenticular degeneration, there were moderate abnormalities of liver function in 6 and severe hepatic dysfunction in 1 case. Franklin and Bauman studied 11 cases of which 7 had clinical signs of hepatic disease and 5 the hepatic type of hepatolenticular degeneration [44] This high incidence of abnormal results of most hepatic function tests in this type of the disease should be anticipated On the other hand, Sweet, Gray and Allen reported unremarkable hepatic function in 9 patients without clinical evidence of hepatic disease.[47]

Leukopenia and thrombocytopenia were the manifestations of secondary hypersplenism in Case 1 It appears that either the chronicity or acuteness of hepatic function is a salient feature in a case of hepatolenticular degeneration Terminally or during transient hepatic insufficiency due, for example, to an intercurrent infection, abnormal hepatic function is more pronounced Otherwise, as in hemochromatosis, needle biopsy of the liver is a better aid than hepatic function tests in the diagnosis of the cirrhosis of hepatolenticular degeneration. Identification of intrahepatic cellular copper deposits in a specimen of cirrhotic liver obtained by needle biopsy and stained by rubeanic acid and alcohol has been recommended



FIG 7a The Kayser Fleischer ring pathognomonic of hepatolenticular degeneration, is more apparent when observed in natural color, and is an opalescent, greenish brown circumferential ring usually 1-2 mm in width, present bilaterally at the periphery of the cornea

TABLE II

Case	Blood Count Complete	Platelets per Cu mm	ESR (Westergren)	A/G gm per 100 cc	BSP % Retention	Bilirubin D/T mg 100 cc	CCF (Units)	TT (Units)	$ZnSO_4$ (Units)	P T (%)	Cirrhosis
1.	WBC 2,500	90,000	35	6.3	11	1.4/2.6	2+	9	—	25	+
2	N	N	22	3.2/3.4	8	0.2/1.4	3+	12.5	22	75	+
3	N	N	8	3.8/2.6	0	0.1/1.0	0	0	11	100	+
4	N	N	12	3.2/3.2	6	0.0/1.4	2+	4	—	100	+
5	N	N	5	3.8/2.6	10	0.0/0.6	1+	2.9	15.2	100	+
6	N	N	7	4.0/2.4	6	0.1/0.9	0	5.5	—	100	+ absent
7	N	N	6	4.2/3.2	5	0.0/0.8	1+	2.1	8.4	67	+
8	N	N	7	3.9/3.2	6	0.1/1.1	2+	5.7	10.2	48	+
9	N	N	—	—	28	2.1	3+	—	—	—	+

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FIG 7a The Kayser Fleischer ring, pathognomonic of hepatolenticular degeneration is more apparent when observed in natural color, and is an opalescent, greenish brown circumferential ring usually 1 2 mm in width, present bilaterally at the periphery of the cornea



FIG 7b A slit lamp photograph of a Kayser-Fleischer ring, 5 mm in width, beginning 1 mm from the corneal margin posteriorly (Courtesy, Rea—Neuro-ophtamology—C V Mosby, Co, 1938)

Other pertinent diagnostic tests in cases of hepatolenticular degeneration are roentgenograms of the esophagus to demonstrate varices, elevated urinary alpha-amino acid nitrogen, copper, glucose and phosphorus, decreased copper-binding protein or ceruloplasmin, and normal or reduced amount of serum copper (Table III). In 3 cases (cases 2, 3, and 9) the total plasma copper varied from 42 to 61 mg./100 ml and the urinary copper varied from 109 to 607 mg /24 hours Amino-aciduria is found consistently in patients with hepatolenticular degeneration and in their families. The significance of the pattern of amino-aciduria awaits further investigation [10 12 84 89] Bearn has studied the renal function of patients with hepatolenticular degeneration and has

TABLE III
PLASMA, SPINAL FLUID, ERYTHROCYTE AND URINE COPPER AND URINE ALPHA AMINO NITROGEN IN 7 PATIENTS WITH *HEPATOLENTICULAR DEGENERATION*

Determination	*Normal Subjects*		*Hepatolenticular Degeneration*	
	Mean	*Range*	*Mean*	*Range*
Total plasma copper ug/100 ml	116	63 161	50	35-65
Direct reacting plasma copper ug/100 ml	8	0 20	26	12-41
Indirect reacting plasma copper, ug/100 ml	108	66-130	24	12 38
Erythrocyte copper ug/100 ml.	115	84-159	129	97 212
Urine copper ug/24 hr	9	0 26	302	115 611
Urine a-amino nitrogen	164	118 204	357	90 519

(Wintrobe, M. M., Cartwright, G. F., Hodges R. E., Gubler, C. J. Mahoney, J. P., Daum, K., and Bean, W. B., Tr. A. Am. Physicians, 1954)

noted resemblance to the de Toni Fanconi syndrome [10,12] Decreased glomerular filtration rate and renal plasma flow, increased filtration fraction and urine pH, and renal loss of bicarbonate were found. Electroencephalograms in 2 of our patients had one diagnostic significance, disclosing only muscular tension. Certain radiological abnormalities of the skeletal system have been demonstrated in patients with hepatolenticular degeneration, possibly as the result of disturbed phosphate metabolism [42] These consist of degenerative joint disease, fractures resembling Milkman's lesions, and osseous fragmentation involving small fragments of bone in the joints of the hands and wrists

CAUSES OF DEATH AND PROGNOSIS

The pertinent contributing causes of death of hepatolenticular degeneration are intercurrent infection (cases 3 and 7), inanition (cases 2, 3, 5), hypersplenism (case 1), esophageal hemorrhage (cases 2, 9), ascites (cases 2, 8, 9), and hepatic insufficiency The brother of case 8 died from a hepatoma

The prognosis of hepatolenticular degeneration depends on the type and severity of the disease The hepatic type survives for one to three years (cases 1 and 9) and lenticular or hepatolenticular type for five to twenty years (cases 2 to 8 inclusive)

TREATMENT

The treatment of hepatolenticular degeneration includes management of the cirrhosis or its complications, the use of chelating

agents in order to decrease the concentration of stored copper in the tissues, and *therapy of the neuropsychiatric manifestations* Cirrhosis, whether it is symptomatic or latent, should be managed in the conventional manner in patients with hepatolenticular degeneration Definitive surgical procedures were a splenectomy in case 1 and a *portacaval shunt in case 2. Exacerbation of neurological* symptoms may appear after an operation leading to death (case 1). Severe dyskinetic phenomenon developed in this case following splenectomy and death occurred two years later.

Several *investigators have reported a specific treatment* of hepatolenticular degeneration with BAL (British Anti-Lewisite, 2, 3-dimercaptopropanol).[33,34,37,41,61,63] During an investigation of the mobilization of copper with BAL in multiple sclerosis, a patient with hepatolenticular degeneration used as a control demonstrated an increase in the already elevated urinary copper level following administration of BAL by Denny-Brown and Porter.[37] This substance was originally introduced by Peters as an antidote against the effects of arsenic gases.[68] They showed that arsenic combined with the sulfhydryl radical in tissue proteins, and BAL competed with the tissues for arsenic, which eventually formed a nontoxic, readily excreted compound. Soon several heavy metals were demonstrated to be excreted from the tissues with BAL. Among them, copper was shown to be effectively excreted in patients with hepatolenticular degeneration, and, in many patients, striking amelioration of nervous symptoms resulted

Denny-Brown and Porter showed that *1.25 to 2 5 mg* of BAL *kg. body weight twice daily for ten consecutive days is the optimum* therapeutic dosage[37] This course should be given monthly or every other month until a steady clinical status is attained. More effective remission of the neurological symptoms will *follow if this therapy is administered early in the clinical course* and continued in intermittent courses depending upon symptomatic neurological relapse. Certain toxic reactions of BAL are sialorrhea, lacrimation, nausea, vomiting, dizziness, pain at the site of the intramuscular injection and amblyopia. A severe anaphylactic attack from BAL occurred in one of our cases. The clinical ameliorative effect of BAL becomes evident ten to four-

teen days after a course of treatment, and persists for one to three months. Not only may tremors, rigidity, dysarthria, gait, and the performance of finer movements dramatically improve, but the color and amount of copper of the Kayser-Fleischer rings temporarily regress In general, BAL therapy has no effect on the clinical or functional and histological status of the cirrhosis The symptomatic response to BAL may be expected to decrease with each succeeding therapeutic course or in advanced cases BAL, by mobilizing tissue copper and augmenting the excretion of urinary copper in cases of hepatolenticular degeneration, converts a positive copper balance to a negative one. Cases 4, 6 and 7 derived temporary benefit from multiple courses of BAL and, in case 9, nervous symptoms were temporarily ameliorated BAL therapy appears to have less remarkable benefit in the acute course of the hepatic type of the disease. Anticholinergic or anti-emetic drugs should be administered to control these parasympathomimetic side-effects of BAL

The oral administration of potassium sulfide effected increased fecal rather than urinary excretion of copper in hepatolenticular degeneration [101] Twenty milligrams of potassium or sodium sulfide was administered three times a day at meal time This drug chelates copper to form insoluble copper sulfide, which is unabsorbed by the gastrointestinal tract The period of treatment has been advocated to range for several months to years A high-protein diet or the intravenous administration of amino acids as 1 liter of 5 per cent casein hydrolysate will enhance the chelating effect of BAL or potassium sulfide [9, 10, 12, 13, 66]

Another chelating agent, calcium versenate, calcium disodium ethylenediamine tetra-acetic acid, is ineffective in cases of hepatolenticular degeneration when administered orally but mobilizes tissue copper minimally upon intravenous administration Wintrobe found the mean excretion of urinary copper over a five-day period in cases of hepatolenticular degeneration to be 253 per cent with BAL, 247 per cent with amino-acid therapy, 500 per cent with combined BAL and amino-acid therapy, 115 per cent with intravenous and 40 per cent with oral calcium versenate, respectively [101] Such measures of mobilizing tissue copper in

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hepatolenticular degeneration, diminishing the absorption of copper from the gastrointestinal tract by chelation or enhancing the excretion of urinary copper, are at best temporary and palliative often with unpredictable beneficial results Ideally, to be effective, such therapy should be continuous rather than intermittent An oral chelating agent penicillamine, 3,3-dimethylcysteine, has been recommended by Walshe to increase the urinary excretion of copper. This substance appears to be the most effective chelating agent to date in the treatment of patients with hepatolenticular degeneration, although it contains only one sulfhydryl radical whereas BAL contains two Restoration of reduced serum ceruloplasm may be accomplished by ceruloplasmin infusions or estrogens but no symptomatic improvement in the disease has been demonstrated Penicillamine gives promise of being an outstanding chelating agent in this condition The dosage is 0 3 gm orally three times daily [21,95,96]

Physical therapy, occupational therapy, employment of newer specific medications for tranquillization, orthopedic appliances, general hygienic measures, and use of the various belladonna-like drugs employed in Parkinsonism or paralysis agitans are adjunctive therapeutic measures Surgical section of the pyramidal tracts, chemopallidectomy, thalamotomy, and pallidotomy for the alleviation of involuntary movements has been reported to relieve these hyperkinetic manifestations in patients with Parkinsonism [30 31 73 103]

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Chapter 12

CIRRHOSIS IN INFANTS AND CHILDREN

INTRODUCTION

THE SUBJECT of cirrhosis in infants and children is paradoxical because these conditions are described often as juvenile, infantile, familial, congenital or metabolic. Some reports do not distinguish cirrhosis from hepatic sclerosis or fibrosis. Such misnomers have limited connotation. Unless the etiological or hereditofamilial factors are known, it is better to classify cirrhosis in infants and children morphologically (Table I). If needle biopsy of the liver is employed more frequently, the identity and transitory states of the hepatic disease may be known more clearly. The pathogenetic factors of diseases commonly associated with cirrhosis in infants and children are malnutrition, viral hepatitis, sickle-cell disease, galactosemia, secondary hemochromatosis, congenital fibrocystic disease of the pancreas, chronic pancreatitis, hepatolenticular degeneration, hepatotoxins, zooparasitic biliary infestation and intrahepatic and extrahepatic obstructive lesions of the biliary tract.

Cirrhosis in infants and children is common in certain parts of the world such as India, Ceylon, Mexico, British West Indies and Africa. Malnutrition and genetic traits may explain this increased incidence.[45,49,50,81,82,122,163,169,178,207,208,213,222] In other parts of the world, the incidence of cirrhosis in infants and children is less than in adults.[53,94,121,148] In 1884, West found cirrhosis in this age group in only 1 of 70,000 patients and only 10 cases in 45 years.[123] Musser's 529 cases accumulated from the literature in 1896 included 400 cases of infantile biliary cirrhosis in India.[121] Keller and Nute found 40 cases of cirrhosis in infants and children in 26 years among 82,866 patients and 2,442 autopsies in the St. Louis Children's Hospital.[123] Some of the early comprehensive data on cirrhosis in infants and children were compiled by Howard in 1887 and Seitz and Schmincke in 1925.[104,123,192,257]

Three pathological types of cirrhosis appeared to be predominant in infants and children biliary, postnecrotic, and portal The etiological factors in these types of cirrhosis appear different from those in adults. Most classifications of cirrhosis in infants and children have been etiological, and have included posthepatitic cirrhosis In 1926, Polynton and Wyllie classified cirrhosis in children as· (1) syphilitic, (2) portal, (a) progressive lenticular degeneration, (b) Banti's syndrome, and (c) associated with or the result of subacute atrophy of the liver, and (3) biliary, (a) Hanot's (b) young children in India, (c) congenital cirrhosis with or without obliteration of the bile ducts, and (d) obstructive biliary cirrhosis [158] A morphologic classification of cirrhosis is quite often meaningless to the pediatrician when an etiological classification is not always possible Keller and Nute and Craig, Gellis, and Hsia have empolyed a combination of etiologic and morphologic classification [42,75,121] This includes posthepatitic cirrhosis, postnecrotic cirrhosis, biliary cirrhosis, portal cirrhosis, hepatolenticular degeneration, hemochromatosis and a multiplicity of rare types of cirrhosis observed in children such as in galactosemia, erythroblastosis fetalis, sickle-cell disease and veno-occlusive disease of Jamaican children Cirrhosis as the result of chronic congestive heart failure is apparently rare, as are those types of cirrhosis in children falling into an unclassified category

It has generally been recognized that there is no sexual predominance in this group of cirrhosis, that the clinical course is shorter than in adults, that congestive splenomegaly and portal hypertension are frequent complications Another significant characteristic of cirrhosis in infants and children is the frequency of its familial and congenital occurrence which has led some observers to conclude that cirrhosis results from more than one pathogenetic factor in a patient [21,149] The familial occurrence of neonatal hepatitis and congenital cirrhosis has been reported in the world literature.[1,14,21,28,42,43,46,57,65,69,79,93,98,103,113,120,123,136,151,194,224] Many of these reports concern cirrhosis other than the type found in hepatolenticular degeneration and erythroblastosis foetalis, which tend to be familial in character.

POSTHEPATITIC CIRRHOSIS

The term posthepatitic hepatitis occurring in infants and children has been employed to describe etiological types of cirrhosis, especially as a sequelae of neonatal hepatitis or viral or serum hepatitis in older children. Hepatitis has been explained by the transplacental transmission of a virus from a healthy mother to fetus, blood group incompatibility, erythroblastosis fetalis, anesthesia and trauma of birth, immaturity of the fetal liver, bacteremia, acquired postnatal viral infection, maldevelopment of intralobular biliary canaliculi, and familial trait.[10, 32, 41-43, 57, 67, 71, 131, 156, 170, 180, 182, 192, 193, 198, 202, 229, 230]

Whereas neonatal or postnatal infectious hepatitis (hepatitis virus I) is a rare condition in infants, it has been demonstrated that serum hepatitis (hepatitis virus S) is reproducible in human volunteers inoculated with sera from either the maternal carrier or infected infant.[147, 198, 199] Neonatal or infantile hepatitis also has been called giant-cell hepatitis. It has been assumed but not confirmed to be due to infection from hepatitis virus I and S.[6, 43, 18-, 193, 231] Erythroblastosis foetalis or maldevelopment of the intralobular biliary canaliculi have also been postulated as pathogenetic factors. Ehrlich and Ratner have reported two siblings with congenital cirrhosis and kernicterus, who died six and one-half hours and forty five hours after birth, respectively.[67] They contend that neonatal hepatitis is related to iso-immunization disease rather than a virus. The familial incidence of giant-cell hepatitis also has been reported.[67, 153] Actually, giant-cell hepatitis refers to a morphological entity rather than a clinical syndrome and has been considered to progress to cirrhosis. Posthepatitic cirrhosis as a sequelae of neonatal hepatitis has been considered to be associated with herpes simplex, viral or serum hepatitis (hepatitis viruses I and S), cytomegalic inclusion disease, giant-cell hepatitis and possible mumps.[157, 161, 162, 193] Cytomegalic inclusion disease is a rare cause of congenital hepatitis, acquired from a mother without evidence of the disease. The disease is assumed to be viral in nature and may progress to cirrhosis.[109, 110, 227] Popper and Volk found an acute toxic hepatitis to be the most common type of hepatitis with jaundice among children.[162] This

disease usually occurred during the course of another bacterial disease. Pathologically, this type of hepatitis is characterized by large multinucleated giant hepatic cells, often containing deposits of iron, preservation of the hepatic lobular architecture, absence of hepatic cellular degeneration and necrosis, moderate

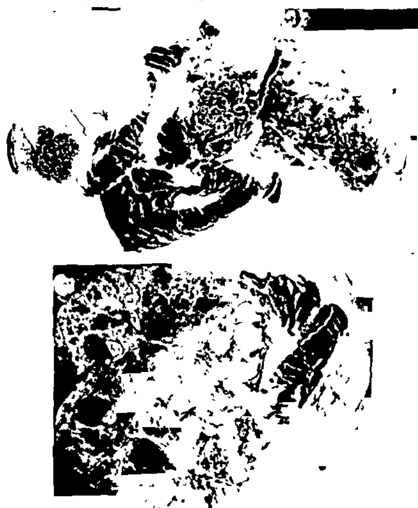


Fig 1a Postnecrotic cirrhosis and congestive splenomegaly Suspected antecedent neonatal hepatitis Note deeply colored liver due to stasis of bile and nodular type of regenerative nodules

Fig 1b Sagittal sections of same specimens

infiltration of the portal area with lymphocytes, bile stasis and variation in the size of the hepatic cells.

Neonatal or giant-cell hepatitis is characterized clinically by jaundice, dark urine, acholic stools, hepatosplenomegaly and hepatic function tests reflective of obstructive jaundice. The prognosis of this condition is grave.[42,43,57,75,82,99,100,116] The transition from neonatal or giant-cell hepatitis to cirrhosis has been reported by several investigators. The development of cirrhosis may be rapid, gradual, or latent following neonatal hepatitis. Gellis, Craig and Hsia found that 11 of 41 infants (27 per cent) developed cirrhosis as the result of this disease.[75] Craig and Landing reported 20 cases of neonatal hepatitis, two of which progressed to cirrhosis.[43] Table 1 shows the clinical data in 7 cases who developed cirrhosis following neonatal hepatitis. The clinical features of this type of posthepatitic cirrhosis may be indistinguishable from neonatal hepatitis. Although posthepatitic cirrhosis may be advanced morphologically, in many cases insufficient time

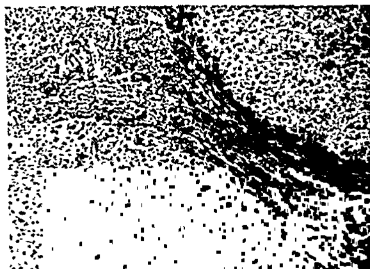


FIG. 2. Histological section of a liver from a nine year old child with post necrotic cirrhosis, who died from hemorrhagic esophageal varices. In addition to the histological criteria of postnecrotic cirrhosis, is stasis of bile. The etiology of this condition was unknown. (H & E, X 120)

had elapsed for the development of the usual clinical signs of cirrhosis Esophageal varices, spider angioma, palmer erythema, loss of weight, ascites, splenomegaly and bleeding tendencies are observed in advanced cases. The presence of normal hepatic flocculation tests in patients with cirrhosis following neonatal hepatitis constitutes the usual finding.

The gross pathological picture of this type of cirrhosis may be either portal or postnecrotic cirrhosis (Figs 1, 2) Nodular regeneration may be underdeveloped and the surface of the liver may be smooth in some cases In these cases, periportal fibrosis, changes typical of neonatal hepatitis, bile duct proliferation, bile stasis, proliferation of fibrosis in the hepatic parenchyma, and inflammatory and degenerative changes in the hepatic cells are observed. The principal causes of death in cirrhosis following neonatal hepatitis are usually hepatic insufficiency and hemorrhage from esophageal varices The age at the time of death ranges from one month to several years In the present series, a child has survived for eight and one-half years following a splenorenal shunt (Fig 3)

Table I shows the clinical findings of cirrhosis in infants and children following infectious hepatitis (cases 8 to 10) and following serum hepatitis (case 11) This variety of posthepatitic cirrhosis is not usually common However, of 27 cases of cirrhosis in children studied by Ruggieri, Baggenstoss and Logan 16 cases (59 per cent) had a history of antecedent hepatitis[176,177] In two instances, cases 9 and 11, hepatitis subsided and eventually cirrhosis developed years later. Hypersplenism was present in case 9, and the physical stigmata were more commonly present in this group than in cirrhosis following neonatal hepatitis In all of the cases and in Gellis' series positive values of hepatic flocculation tests were present.[42,75,114] Survival ranged from several months to a year. Death was due to hepatic insufficiency and esophageal hemorrhage The surviving cases are presently doing well Six of eight cases in this category reported by Gellis died, two from sepsis, two from bleeding esophageal varices, and two from ascites and hepatic insufficiency In this group, postnecrotic cirrhosis is commonly found. These livers are usually atrophic, coursely



Fig 3a This was diagnosed so-called "congenital cirrhosis" Hepatosplenomegaly hypersplenism esophageal varices abdominal collateral venous circulation Successful splenorenal surgical shunt was performed, but death occurred several years later from recurrent hemorrhagic esophageal varices

nodular and do not differ morphologically from the adult variety [139] Postnecrotic cirrhosis in infants and children may also be due to exposure to hepatotoxic agents (case 22)

BILIARY CIRRHOSIS

There are several types of biliary cirrhosis encountered in infants and children They may be classified as follows

- A Primary biliary cirrhosis (intrahepatic)
  1. Cholangiolitic cirrhosis
  2. Acholangitic cirrhosis (atresia of intrahepatic biliary ducts)
  3. Congenital
- B Secondary biliary cirrhosis (extrahepatic)

1 *Developmental defects*
   a Atresia of extrahepatic biliary ducts
   b Choledochal cyst
2 Acquired obstructive lesions· gallstones, tumors, stricture, xanthomata, parasites, lymphodenopathy, etc.

C. Infantile biliary cirrhosis (India, North China, and Mexico)
D Biliary cirrhosis of cystic fibrosis of the pancreas

The reader is referred to Chapter 8 and 9 for detailed discussions on primary biliary cirrhosis and secondary (obstructive) biliary cirrhosis

The most common cause of biliary cirrhosis in Caucasians is congenital atresia of the biliary system tract It has been noted that biliary cirrhosis occurs frequently in congenital obstruction of the biliary system and infrequently after chronic biliary obstruction in adults This lesion may be partial or complete, localized or involve completely the intrahepatic and extrahepatic biliary tract, resulting in obstructive jaundice and biliary cirrhosis. The cause of atresia has been postulated to be viral, toxic damage,

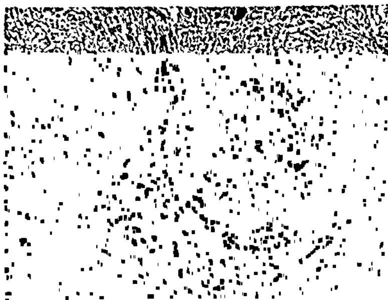


Fig 3b Surgical biopsy of this liver. Nodular regeneration, increase in fibrous connective tissue, hepatocellular necrosis, and stasis of bile, gross morphological appearance of portal cirrhosis (H & E, X80).

anomalous absence, or embryonic occlusion of the bile ducts as the result of failure to recanalize during the fourth and fifth months of fetal development.[62, 64, 80, 92, 111, 116, 129, 130, 132, 174, 216] In 1891, Thomson described nearly thirty types of atretic malformations of the hepatic, cystic and common bile ducts[203a] Rolleston and Hayne in 1901 considered biliary cirrhosis the primary lesion resembling Hanot's cirrhosis and the atretic lesions of the bile ducts secondary[174] Holmes reported 100 cases of biliary cirrhosis due to congenital obliteration of the bile ducts up to 1916[111] In 16 per cent of 51 cases that he reviewed, the extrahepatic ductal system appeared normal and communicating He described quite accurately the embryological aspects and added several types of malformations to Thomson's original sketches of congenital atresia of the bile ducts He described the clinical picture of this type of biliary cirrhosis as being predominent in male infants with jaundice, ecchymoses and hepatosplenomegaly In place of the extrahepatic bile ducts, there was loose connective tissue in which lay the hepatic blood vessels, nerves and a cord-like rudimentary gallbladder often containing green black bile and mucus Ladd in 1935 classified congenital obstruction of the bile ducts on the basis of 15 cases: (1) absent extrahepatic bile ducts; (2) atresia of hepatic ducts, (3) atresia of common bile duct, (4) cystic remnant of the gallbladder which may be disconnected with the common bile duct or hepatic ducts, if they are present, (5) anomalous anastomosis between the gallbladder and the duodenum in the absence of the extrahepatic bile ducts, (6) stenotic common bile duct Many additional studies of the various lesions of congenital obliteration of the biliary system and the common bile duct obstructed by inspissated bile, and their surgical amenability have been made It is known that biliary atresia may occur in families Congenital atresia of the biliary system may be associated with other developmental anomalies especially congenital cardiac[6]

The gross pathological appearance of the liver in congenital atresia of the extrahepatic bile ducts is an enlarged, dark green, finely granular cirrhosis (Fig 4)[69, 132] The size of the regenerative nodules simulates portal cirrhosis Dilatation of the intrahepatic bile ducts and hydrohepatosis are observed in sagittal sec-







tions of the liver (Fig 5). Hepatocellular degeneration, intracellular and intraductule stasis of bile, proliferation of bile ducts in the portal regions, cholangitis, interlobular inflammatory changes and fibrosis, and cirrhosis are histopathological changes in the liver [42,152] Only 2 of 47 livers studied pathologically by Craig and his coworkers were not enlarged and no correlation was found to exist between the degree of hepatic enlargement and the duration of life [42] They have shown that only after two years of age do the livers in instances of atresia of the extrahepatic biliary tract display true regenerative nodules In 33 cases studied at necropsy, they found ascites present in 11 cases, esophageal varices in 4 cases and enlarged spleens in 13 cases.

The clinical findings in this type of biliary cirrhosis are obstructive jaundice beginning at birth, dark urine, light stools, markedly enlarged liver, and moderate enlargement of the spleen Patients who are not amenable to surgery survive from 6 to 15 months Survivals have been recorded in patients whose lesions are uncorrectable who were 5 to 12 years old [123,152,221] Ascites, portal *hypertension and hepatic failure are late manifestations* Xanthomatosis, hypercholesterolemia, and hyperphospholipidemia may occur in this condition [2,4,157,138]

The duration of life appeared related to the presence of clinical cirrhotic manifestations The longer these patients live, the more frequent splenomegaly, portal hypertension, ascites, esophageal varices, and other cirrhotic stigmata become apparent Biliary cirrhosis in patients with congenital atresia of the bile ducts is characterized by several interesting features as Myers and co-workers have demonstrated [152] These are the rapid development and frequent occurrence indicative of the marked regener-

FIG 4a Specimen of liver and spleen from a fatal case of secondary biliary cirrhosis due to complete atresia of the common bile duct Note dark hepatosplenomegaly due to stasis of bile in both specimens and also chronic passive congestion of the spleen

FIG 4b Histological findings of liver of Figure 4a Note large dilated intrahepatic bile ducts, regenerative nodules demonstrated probably trabeculae, hepatocellular degeneration, marked round cell infiltration and stasis of bile (H & E, X50)

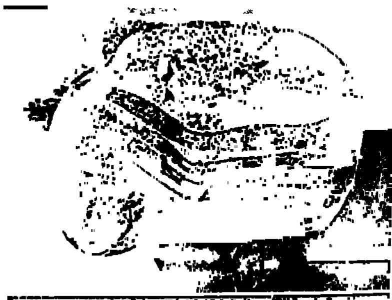
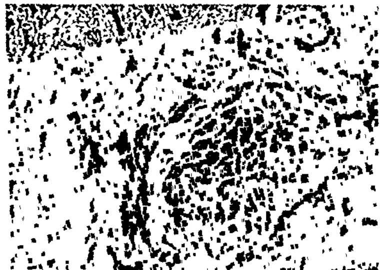




Fig 5a Specimens of transected liver and spleen Secondary biliary cirrhosis due to atresia of extrahepatic bile ducts Congestive splenomegaly, the liver demonstrates a finely granular surface, moderate fibrosis, hydrohepatosis, enlargement, and dark green pigmentation

Fig 5b Inferior aspect of a gross liver from a case of atresia of the common bile duct Death due to hepatic insufficiency Marked cholestasis and enlargement are present without secondary biliary cirr[illegible]

ative capacity of the infantile liver in response to complete biliary obstruction in comparison to the secondary or obstructive biliary cirrhosis in adults, which is an uncommon lesion. Cirrhosis was present in 18 of 21 livers in Myer's series, and, in 3 instances where cirrhosis was absent, a surgically amenable part of the extrahepatic biliary tract was available. This suggested to the group that an additional factor accounts for the presence of cirrhosis in this condition, namely, the completeness of the atresia biliary tract. Four of Craig's five cases died from hepatic insufficiency. Laboratory tests indicate obstructive jaundice, and in the eventual clinical state abnormal hepatic flocculation values are present. Hsia and Gellis have disclosed that serial serum bilirubin determinations are the most helpful function test in diagnosing prolonged obstructive jaundice in children.[114] A slowly rising serum bilirubin suggests biliary atresia, a rapidly falling one hepatitis or erythroblastosis fetalis, and a slowly falling one, an inspissated-bile syndrome.



F ... secondary biliary cirrhosis ... ra ... mon bile duct. Nodular regeneration, hepato... marked fibrosis, generalized stasis of bile, dilated, reduplicated, inspissated intrahepatic bile ducts and biliary canaliculi. (H & E, X50)

The operative rate for patients with congenital atresia of the biliary tract is approximately 25 per cent [92, 111, 130] It is apparent that if the atretic lesion is to be corrected, an operation should be performed as early in the clinical course as possible Myers and his coworkers have noted that biliary cirrhosis became advanced rapidly. [152] They also found that the absence of cirrhosis frequently, but not exclusively, is associated with surgically correctable atretic lesions of the biliary tract Consequently, information obtained from an hepatic biopsy and hepatic flocculation tests may confirm the presence of cirrhosis and be of prognostic value The presence of extrahepatic biliary ducts continuous with intrahepatic biliary ducts sufficient for surgical anastomosis to the duodenum, jejunum, or stomach is another important therapeutic consideration [89] Longmire and Sanford's operation, which consists of partial left hepatic lobectomy and intrahepatic jejunostomy, has had limited success in patients with congenital atresia of the extrahepatic biliary ducts because dilated intrahepatic bile ducts are observed infrequently in this condition [92] Operative cholangiograms, exploratory laparotomy of the biliary tree, and hepatic biopsy offer diagnostic and prognostic benefit and differentiate this condition from other causes of infantile obstructive jaundice, particularly chronic parenchymal damage [106, 203, 241]

Biliary cirrhosis may develop in infants and children from congenital atresia of the intrahepatic bile ducts Ahrens and his coworkers in 1951 reviewed the literature on this subject and reported in detail the clinical and pathological data in 4 cases [2] They credit Heschl in 1865 as the first to report this condition Up to 1957, 15 cases of atresia of the intrahepatic bile ducts had been reported [2, 158] The gallbladder and extrahepatic biliary tract may be absent, rudimentary, or normal in this condition Clinically and biochemically, congenital atresia of the intrahepatic bile ducts or its accompanying biliary cirrhosis is indistinguishable from atresia of the extrahepatic bile ducts and secondary biliary cirrhosis The only unfailing distinction is the histological identification of intrahepatic bile ducts in the latter condition. Pathologically, the liver in this condition constitutes the various stages of secondary biliary cirrhosis (Chapter 9). Histologically, the absence of intrahepatic bile ducts is essential for the diagnosis this type of biliary cirrhosis

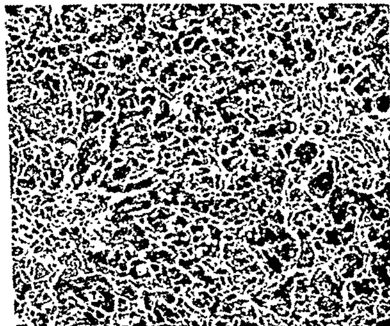


Fig. 6. Morphological appearance at abdominal laparotomy of biliary cirrhosis due to atresia of the intrahepatic bile ducts. Note absence of bile ducts in portal areas. Otherwise, there are histological findings of biliary cirrhosis, although nodular regeneration is absent in this field. (Courtesy Peace, R. J.)

(Fig. 6). The portal areas disclose arteries and veins but no bile ducts. Ahrens failed to locate biliary epithelium in the histological examination of more than 700 portal areas in 1 cases. The portal areas also contain increased fibrous connective tissue without inflammatory cells. Bile canaliculi are dilated containing inspissated bile and the hepatic cells are bile-stained.

The clinical picture of this disorder is obstructive jaundice, dark urine, light stools occurring at birth, impaired growth, marked smooth hepatomegaly and, occasionally, splenomegaly, pruritus, osteomalasis, osteoporosis, dry skin, steatorrhea, bleeding tendency, petechiae, kernicterus and cutaneous xanthomatosis. This obstructive jaundice is variable in this condition has suggested to Ahrens that the hepatic lymphatics may act as accessory channels

to excrete bile during biliary obstruction. The clinical picture is indistinguishable from primary biliary cirrhosis. Xanthomatosis of the skin appears only after eighteen months of age implying reasonably good hepatocellular function. With this complication, hypercholesterolemia, hyperphospholipidemia and clear serum are demonstrated. In addition, the laboratory picture is compatible with obstructive jaundice and hypoprothrombinemia. The duration of life varies from eighteen months to over five years. Death is the result of malnutrition and hepatic insufficiency.

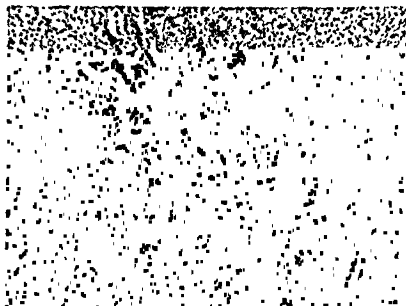


FIG. 6b. Histological findings from a case diagnosed preoperatively as obstructive jaundice probably on the basis of atresia of the biliary system. It was determined at surgical operation that there were no obstructive lesions of the entire biliary system. A coarsely nodular cirrhosis was found, but with minimal bile pigmentation. Clinically, hepatic function tests suggested obstructive jaundice and chronic liver damage (cirrhosis?). Histologically, postnecrotic cirrhosis was established.

Another rare type of biliary cirrhosis observed in infants and children is primary or cholangiolitic biliary cirrhosis. The clinical picture and pathologic features are identical with the adult type. Cooray and Panabokke have reported 3 cases in children between



Fig 7a Histological picture of primary biliary or cholangiolitic cirrhosis in a *seven year old child Needle biopsy of the liver* very little *chronic* pericholangitis stasis of bile and focal hepatitis The transient hepatic status was speculated (H & E ×80)

one and one-half and two years of age and Peace 4 cases under three months of age [illegible] Two cases of this condition were observed recently in children In neither case was nodular regeneration present in the needle biopsy of the liver Histologically, a severe and slight pericholangiolitis was present in 1 case (Fig 7) The clinical picture in children is indistinguishable from that seen in atresia of the intrahepatic or extrahepatic bile ducts Insufficient follow-up in the course of patients with juvenile primary biliary cirrhosis exists at the present time Surgical exploration of the extrahepatic biliary system, operative cholangiography and needle biopsy of the liver, in particular, for the recognition of intrahepatic bile ducts appears essential before this diagnosis can be entertained

A peculiar type of nutritional cirrhosis is infantile biliary cir-

rhosis, found especially in India, Mexico, and North China[76 78 74 136 151 155 163 165-168 174 159 204] The disease was reported first by Sen in 1887 and studied extensively by Ghose in 1887, Gibbons in 1887 and P Krishna Rao in 1931 and 1941. So prevalent was infantile biliary cirrhosis in India, particularly in the Mysore State, that the government undertook a special survey of the incidence in 1931. Two etiological factors have been postulated to account for the disease, namely cow's milk and the coliform bacillus or E. Coli. It has been suggested that cow's milk brings about the predisposing factors of the disease "gastrointestinal disorder and devitalization of the liver, and E Coli completes the pathological process "[78 87 90 128 168] Infantile cirrhosis has not been observed in patients fed on breast milk or substitute "infant milk foods"

The liver of this type of infantile cirrhosis has been described as a biliary cirrhosis, a portal cirrhosis, and as a subacute toxic cir-

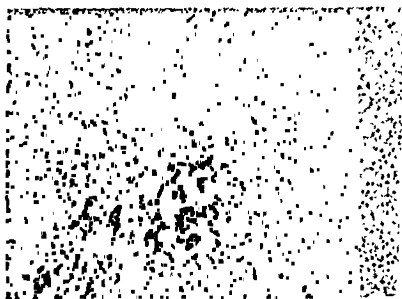


FIG 7b Surgical biopsy of the liver of an eleven year old boy with clinical features of primary biliary (cholangiolitic) cirrhosis of five years duration having established patent extrahepatic biliary system and clinical findings suggestive of this condition except slight abnormalities in the flocculation tests Grossly and histologically, it was considered a postnecrotic cirrhosis of unknown cause Severe obstructive jaundice and pruritus

rhosis. P. K. Rao states that the gross and histopathological appearance of the liver is undoubtedly portal or Laennec's cirrhosis.[186] Gibbons classifies the liver as biliary cirrhosis and emphasizes among several morphological features the smooth, finely granular surface, bile stained parenchyma, proliferation and ramification of bile ducts in the stroma, nodular regeneration, hepatic cell degeneration and increase in fibrous connective tissue.[79] Radhakrishna Rao considers this type of cirrhosis unique, designating the condition as subacute toxic cirrhosis.[187] The primary lesion is in the hepatic venous tree due to phlebosclerosis, endophlebitis and partial thrombosis. Nodular regeneration is retarded, hepatocellular necrosis is uniform and variable, and pseudo-lobules are very small (Fig. 8). In India it has been observed in Hindu children between the ages of six months and three years and among families even in the upper social class who are vegetarians. The onset is usually insidious and by the time the symptoms are apparent, the condition is advanced. Initially, these are voracious appetite, occasionally vomiting, and intermittent periorbital and pedal edema. The second stage begins with impaired appetite or craving for food especially sweets, nausea, vomiting, constipation, enlargement of the abdomen, thirst, irritability, fever, lethargy, loss of normal skin color, and a burning sensation of the hands and feet. Examination reveals firm and marked enlargement of the liver, abdominal collateral veins, low-grade fever, occasionally an enlarged spleen, and a low-grade jaundice. This stage persists for three to six months. The third stage is characterized by contraction of the liver, causing abdominal pain, anasarca, jaundice, oliguria, hypochromic anemia, leukocytosis, elevated temperature, evidence of portal hypertension in the form of esophageal varices and genitourinary hemorrhage. Death is usually due to hepatic insufficiency, bleeding esophageal varices or intercurrent infections. The pertinent laboratory features are marked leukocytosis, lymphocytosis and hypoglycemia.

PORTAL CIRRHOSIS

Portal or Laennec's cirrhosis in infants and children particularly has little connotation and implies a morphological feature or a cryptogenic, malnutritional, or posthepatitic cirrhosis. Although

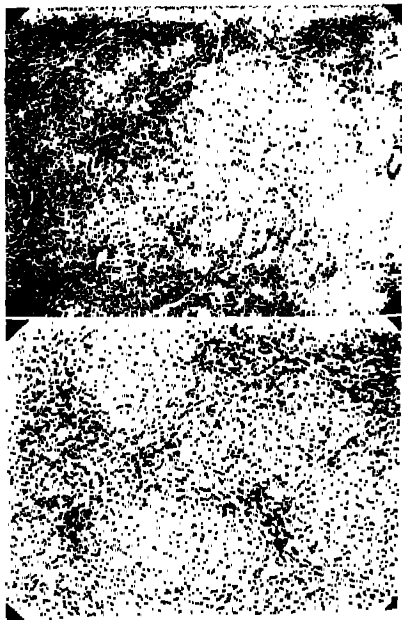


Fig 8a Infantile cirrhosis of India Low power view of the section of the liver, shows distinct lobulation of the liver—"multilobular variety" dilation of the portal veins and necrosis of the hepatic cells (Courtesy, Rao, P. Krishna—Proceedings of the Indian Academy of Sciences—1941)

it is the commonest type of cirrhosis in adults, portal cirrhosis is very uncommon in infants and children Moon in 1935 mentioned 120 cases of portal cirrhosis in children reported by Sertz in 1921 and reported on an additional 90 in the literature [150] Biliary, post hepatitic and postnecrotic are the most common types of cirrhosis in children In 17 cases where the gross pathological type of cirrhosis was determined, portal cirrhosis was seen in only 1 instances (Fig 8) Ocassionally, portal cirrhosis may be a sequelae of viral hepatitis in infants and children Portal cirrhosis has been reported to occur in families [29, 93, 123, 130, 202] Several etiological factors have been considered These are nutritional deficiency, anemia, helminthic infestation and bacterial infections as observed in the fatty liver syndrome in Ceylon and the British West Indies [34] Moon considered portal cirrhosis in children to be the result of several etiological factors, infection being the most predominant

Weakness, loss of appetite, occasional jaundice, and loss of weight are the early symptoms Eventually, ascites, edema, a hard enlarged liver, malnutrition, splenomegaly, bleeding tendencies and esophageal varices develop Hypersplenism is very common in portal cirrhosis in children The clinical course of portal cirrhosis in children is shorter than in adults As expected, hypoalbuminemia, hyperglobulinemia, and abnormal values for hepatic flocculation tests are present in the eventual clinical course Death is due to bleeding esophageal varices, intercurrent infection, and hepatic insufficiency Actually, except for the increased incidence of hypersplenism and abbreviated clinical course, the pathological picture of portal cirrhosis in infants and children is identical to the adult form

KWASHIORKOR

Kwashiorkor is a nutritional disease found predominantly in poverty-stricken infants and children in the tropics and is characterized by retarded growth and development, dermatoses, mental

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Fig 8b Infantile cirrhosis of India High power view of the section of the liver Formation of pseudolobulation and fibrous tissue, particularly at the portal spaces and distortion of the normal architecture of the lobules are clearly seen Mallory's Stain (Courtesy, Rao, P Krishna—Proceedings of the Indian Academy of Sciences—1941)

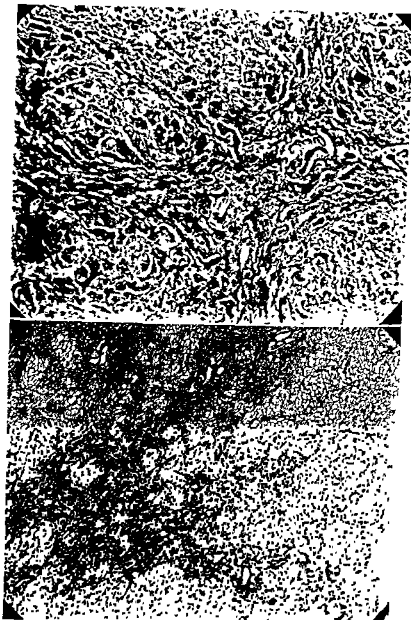


Fig 8c Infantile cirrhosis of India Bile Capillaries in the portal spaces Extensive ramification of bile capillaries in the portal spaces H & E Stain (Courtesy, Rao, P Krishna—Proceedings of the Indian Academy of Sciences—1941)

apathy, frequent intercurrent infections, dyspigmentation of the hair and skin edema, cardiac atrophy, diarrhea, steatorrhea, fatty liver and a large mortality in the absence of proper dietary treatment (Fig. 10a). Kwashiorkor is found in Africa particularly along the Gold Coast and means "Red Dog." It is also known as "malignant nutrition," "infantile pellagra or edema," in the Orient, "Mehlnährschaden" or "starch or flour dystrophy" in the Far East and Africa, "nutritional edema" in Europe, "síndrome pluricarencial de la infancia" in Spanish speaking countries, "fatty liver disease" in Jamaica, and "culebrilla" in Mexico, and "edematous multiple deficiency syndrome" in Central and South America. The reports and textbook by Trowell, Davies and Dean *Kwashiorkor* and others give detailed historical, clinical and pathological descriptions of this disease.[11,14,31,48,52,107,108,151,153,207-212,215,219,222,223]

Most authorities consider that infants with this condition are born from malnourished mothers with a poor constitutional background. Protein malnutrition appears primarily responsible for the development of kwashiorkor, and is often associated with multiple avitaminosis. This disease begins rapidly with weaning. This may be reflected when weaning either begins late as seen in the tropics or takes place when another child is born and supplants the elder on the breast. Thus, the newly weaned child is shifted from a poor protein diet to one containing carbohydrate and roughage almost exclusively. Acute episodes of kwashiorkor in a malnourished child may be precipitated by infectious diarrhea, exanthematous diseases, starvation, and economic disaster.[93,94,144-154]

Because of the low amount of protein in the mother's breast milk, the disease actually begins in infancy and is augmented at the time of weaning. Dermatitis, dyspigmentation of the skin and hair, and arrest in growth and development may begin even during breast feeding. Diarrhea, steatorrhea, digestive intolerance to fat or starch, lethargy, irritability, restlessness, muscular wasting, impaired appetite, nausea and vomiting are present. "Crazy pave-

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Fig. 8d. Infantile cirrhosis of India. Low power view of the silver impregnated section. Extensive formation of collagen fibers, particularly at the portal spaces. Rio Hortega's Stain. (Courtesy, Rao, P. Krishna—*Proceedings of the Indian Academy of Sciences—1941.*)



Fig 9a Typical histological picture of portal cirrhosis Needle biopsy of liver, eleven year old male with chronic ulcerative colitis for at least five years The clinical status of both conditions at the time of biopsy was relatively inactive (H & E, X60)

ment" or "enamel-paint dermatosis" are terms employed to describe the severe skin lesions mostly on the pressure or flexural areas which may become infected or ulcerate easily The consequence of the low-protein diet manifests itself in dystrophy of the exocrine glands, the pancreas, stomach, small intestine, and salivary glands resulting in pancreatogenous steatorrhea, gastric achylia, macrocytic anemia, and features of the malabsorption syndrome. Fatty liver, due to protein malnutrition or pancreatic fibrosis occurs Enlargement of the liver and spleen are present, and Davies had shown that despite the cirrhosis in older children, clinical evidence of portal hypertension is lacking [49, 51] The disease may also occur in adults in which case the course is less relentless and ascites, edema, gynecomastia, and testicular atrophy suggest cirrhosis.

The liver of kwashiorkor varies with the age of the patient and duration of the disease. In young children, there is seen an extensively fatty liver, which is enlarged, pale, and yellow, and eventually a stellate hepatic fibrosis (Fig 10b). In older children who sur-

vive, cirrhosis may be present and fatty infiltration of the liver diminishes. Perusal of pathological reports of the liver of kwashiorkor suggests that, as the condition progresses, hepatic fibrosis rather than cirrhosis becomes evident. Only in older children or adults, where, in fact, the disease is least common, may valid cirrhosis occur. The liver may resemble the nutritional, portal cirrhosis. Davies has noted postnecrotic cirrhosis in older children surviving from kwashiorkor.[45] The term "Red Dog" implies a change in color of the hair from black to brown, red, or blonde, which becomes soft and falls out. A desquamating dry dermatitis, cutaneous hypopigmentation, abdominal distention, stunted growth, fever, edema, ascites and physical findings of avitaminosis, particularly A, B, and D, also accompany this condition. Davies has emphasized that cirrhosis should not be considered a characteristic of kwashiorkor in children, and, in fact, questions the direct transi-

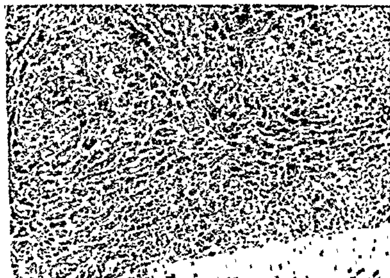


FIG. 9b. Histological finding ... year old boy who died from pulmonary tuberculosis ... malnutrition. Chronic liver disease was not suspected clinically. This picture shows the edge of a larger regenerative nodule, stroma, hepatocellular necrosis, and centrilobular passive congestion. No evidence of hepatic tuberculosis was found. (H & E, X80)

tion from fatty liver in this condition to cirrhosis [49] Malnutritional hemosiderosis may be associated with kwashiorkor in the Bantu tribe as the Gillmans have shown but not in the Ugandas [81-82] It



Fig. 10a Kwashiorkor in an infant Note malnutrition, depigmentation and dermatitis (Courtesy, Davies, J N P—Department of Pathology—Makerere College Kampala, Uganda)

may be that this is the result of cooking food in iron pots (Chapter 10)

The important laboratory findings found in kwashiorkor are macrocytic, normochromic anemia, hypoalbuminemia, hyperglobulinemia, abnormal values of hepatic flocculation tests hypocholesterolemia and hyperlipemia, quantitative increases in the amount of stool fat and nitrogen, hypokaliemia, diminished amount of pancreatic enzymes, and a nutritional deficiency or sprue pattern in the x ray of the small intestine Death may be attributed to intercurrent infection, marasmus, and hepatic coma

The prognosis of untreated cases of kwashiorkor is poor and the infant mortality is high Those who survive develop hepatic fibrosis and possible cirrhosis or primary carcinoma of the liver. Treatment of kwashiorkor is the substitution of a high-protein diet which produces marked amelioration of the symptoms [222,224] The Gillmans



Fig. 10b Histological findings of a liver with Kwashiorkor marked fatty infiltration (H & E X80) (Courtesy Davies J N P —Department of Pathology —Makerere College Kampala Uganda)

have treated this condition with 10 gm./day of powdered stomach administered orally, which reversed the fatty liver and prompted diuresis.[83] Adjunct vitamin therapy is also recommended.[29] The results from the administration of dessicated stomach, vitamin, or lipotropic therapy are inconsistent.

VENO-OCCLUSIVE DISEASE OF THE LIVER

Veno-occlusive disease of the liver is a nonportal cirrhosis, often familial, occurring frequently in Jamaican, African and Indian children and occasionally in adults. Diets deficient in protein and the use of "bush teas" containing toxic Senecio alkaloids either medically or as food have been found to be the cause of this syndrome in malnourished patients.[25,26,107,109,119,171,172,188,197,200,201,225]

Stuart and Bras have divided the clinical course into three stages. The first is characterized by sudden abdominal pain, enlargement of the liver, ascites and often vomiting, splenomegaly and edema. Children between the ages of eighteen months and three years are affected commonly, and Rhodes has mentioned the disease may be precipitated by the usual childhood diseases.[171,200,201]



FIG 11a Specimen of liver with cirrhosis in chronic veno-occlusive disease Morphological details unknown, but note coarse nodularity and broad, deep scars (Courtesy, Bras, G—University College of the West Indies—Jamaica, British West Indies)

While most patients recover, some die from hepatic insufficiency. The subacute stage, which may be apparent from the onset, is characterized by an enlarged liver, recurrent ascites sometimes, and splenomegaly. Generally, nutrition is maintained and jaundice is rare. In the chronic stage, the clinical features are similar or indistinguishable from cirrhosis. Death is due to ruptured esophageal varices or hepatic insufficiency. Hepatic function tests, particularly determination of the serum albumin and cholinesterase, become progressively impaired as the disease progresses.

Histologically, the liver in patients with veno-occlusive disease discloses subintimal thickening, stenosis, and occlusion of the hepatic veins, dilatation of the sinusoids, parenchymal congestion, and condensation and an increase in reticula fibers in the centrilobular areas (Fig. 11). Eventually, the liver progresses to a cirrhosis similar to the postnecrotic variety. It has been implied that the fluctuation of occurrence of ascites in veno-occlusive disease of the liver, regardless of the presence of cirrhosis, is related to intrahepatic block of the hepatic veins and capillary permeability.

Treatment of this disease is conventional and a diet consists of high amounts of protein but restricted in sodium.



Fig. ... ...uded branch of hepatic vein ... in the periphery in chronic veno-occlusi... ...ease, X150) (Courtesy Bras, G., Jelliffe, D. B., and Stuart, K. L.—Arch. Path.—April 1954.)

GALACTOSEMIA

Galactosemia is an uncommon congenital metabolic condition occurring in infants and children. It is characterized by impairment in growth and development, malnutrition, enlargement of the liver, mental retardation, cataracts, osteoporosis, albuminuria, hypoglycemia, hypergalactosemia and galactosuria. The disease may be familial The disease represents an inability of the body to metabolize galactose normally.[112] The marked impairment of galactose metabolism is demonstrated by elevated galactose in fasting

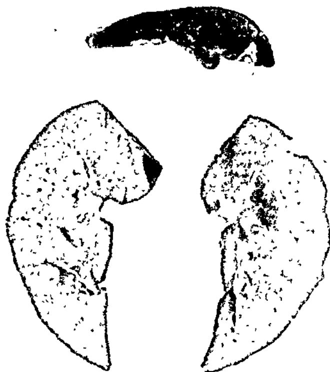


Fig. 12a Specimen of a liver with cirrhosis in galactosemia Infant two months old, liver (*below*) weighing 150 gm; red pulp is prominent and increased fibrous connective tissue in spleen (*above*). (Courtesy, Edmonds, A. M, Hennigar, G R., and Crooks, R.—Pediatrics—July, 1952)



...ate the hepatic lobules. ... peculiar acinar structures contain bile ... Edmonds A M, Hennigar G R, and Brooks R — Pediatrics—July, 1952.)

blood and prolonged retention of galactose in the blood after an intravenous galactose tolerance test. The clinical course may be acutely fatal, marked by malnutrition, protracted for several years with gradual loss of intolerance to galactose, or mild, in which case some galactose is metabolized eventually. In the protracted clinical course, malnutrition and signs and symptoms of hepatic damage may occur.

Galactosemia was first described by Von Reuss in 1908 in a malnourished, maldeveloped eight month old infant whose liver at autopsy revealed cirrhosis.[215] He was disinclined to call this galactosemic cirrhosis because the infant had been given cognac since birth. Up to 1952, the literature revealed 26 reported cases of galactosemia.[34, 35, 66, 208]

Various types of hepatic injury, hepatocellular jaundice, hepatosplenomegaly and hepatic dysfunction are prominent features of this disease. This includes a fatty liver morphologically similar to the adult type of malnutritional or diabetic fatty liver, hepatic fib-

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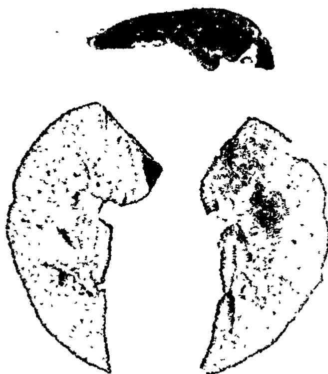


FIG 12a Specimen of a liver with cirrhosis in galactosemia. Infant two months old, liver (*below*) weighing 150 gm, red pulp is prominent and increased fibrous connective tissue in spleen (*above*). (Courtesy, Edmonds, A M, Hennigar, G R., and Crooks, R.—Pediatrics—July, 1952)



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rosis and cirrhosis and abnormalities of the bromosulfalein retention, serum Van den Bergh, hepatic flocculation tests, and prothrombin value.[12,14,30,42,63,85,86,118,145,153] This suggests that the liver is the main organ of the body with physiological and morphological changes as the result of galactosemia and that this organ may be the primary site of the metabolic defect.

Komrower has found a marked amino-aciduria in patients with galactosemia and has suggested that galactose-1-phosphate is the toxic hepatic agent.[126] Isselbacher and his co-workers provided evidence that congenital galactosemia represented a defect or lack of Pgal-uridyl transferase,[117] one of four specific enzymes involved in galactose metabolism of human hemolyzates. It has been suggested: (1) that an idiopathic enzymatic disturbance in galactose metabolism produces excessive deposition of fat and glycogen in the hepatic cells, (2) congenital fatty cirrhosis or malformation of the liver, and, (3) congenital disturbance in bile excretion producing hepatocellular damage are three possible mechanisms causing hepatic damage in galactosemia [14,66,206] Hypoglycemia, amino-aciduria, and the toxic action of galactose in hepatic cells, have been considered as causative factors of hepatic disease in this condition [30,115,145,153]

Cirrhosis occurring as a complication in patients with galactosemia has been described differently. Portal or fatty cirrhosis has been reported by several authors [15,63,206,213] A distinctive variety unlike the portal or biliary variety cirrhosis has been reported by another group.[12,42,66,118] In the latter type of cirrhosis, histological examination reveals "gland-like structures, adenomata, bile stasis and bile thrombi, granular nodular regeneration, fine stroma, and hepatic cells which are vacuolated, "blown-up" or contain excessive deposits of fat, glycogen or bile (Fig. 12).

GLYCOGEN-STORAGE DISEASE (VON GIERKE'S DISEASE)

In 1929 von Gierke described a disease, often familial, occurring in infants and children which results from a congenital defect in carbohydrate metabolism, and is characterized by the extensive deposition of glycogen in the liver and kidney and impaired glycolysis [214] Glycogen-storage disease has been classified into several categories [8,9,39,74,127,133,140,142,169] Type 1 refers to classical von

Gierke's disease or hepatorenal glycogenosis, due to deficiency of glucose 6-phosphate. Type 2 reported by Anderson includes glycogen-storage disease of the liver and reticuloendothelial system due to a deficiency of the "branching enzyme," amylo (1,4-1,6) transglucosidase as postulated by Cori.[39] Anderson has seen 4 cases of this type occurring in siblings having cirrhosis. Type 3 is glycogen-storage disease of the liver with cirrhosis, presumably due to deficiency of the debranching enzyme. Type 4 is glycogen storage disease of the heart with generalized glycogenosis of unknown origin. Type 5 is cryptogenic glycogen-storage disease of the striated muscle without cardiomegaly. Types 2, 3 and 4 may be familial. [9]

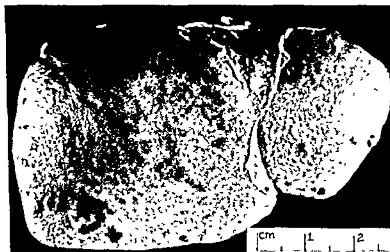


FIG 13a Specimen of the liver with so-called congenital cirrhosis of the liver. Kernicterus, sequela of neonatal hepatitis, suspected relationship to iso-immunization disease, cirrhosis (weight 40 1 gm) (normal 66 3 gm) superior surface studded irregularly with coarse and fine isolated nodules (Courtesy, Ehrlich, J C, and Ratner, I M — Am J Path —1955)

Cirrhosis, hepatoma and glycogen-storage disease has been reported by several investigators[9 42 74 103 133 141 169] Anderson has described cirrhosis in a seventeen month old child with Type 2 glycogen-storage disease whose liver weighed 560 gm. (normal

331 gm.).[6] The patient's brother had previously had cirrhosis and glycogen-storage disease. The liver was described as being hard, finely granular, glistening and yellow- to buff-colored. Histological examination of the liver disclosed nodular regeneration, increase in fibrous connective tissue, and hepatic cells which were large, vacuolated, multinucleated, and contained a granular cytoplasm which were stained for glycogen with Best's carmine stain. Biopsy of the liver revealed abnormal structure of the glycogen with fewer branches and longer outer chains than normal human glycogen. Ascites, diarrhea, fever, anorexia, jaundice, marked hepatosplenomegaly and emaciation were observed in this patient.

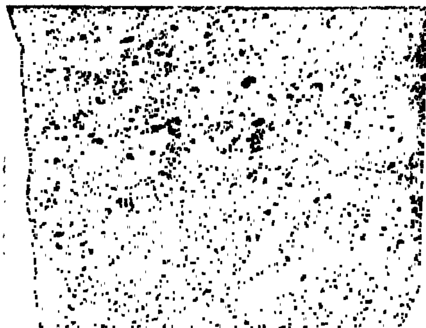


Fig. 13b. Histological picture of the liver from the same case, fibrosis, stasis of bile, hepatocellular necrosis, early nodular regeneration. (H & E, X32)

Bridge and Holt have described the hepatic form of glycogen-storage disease.[27] Pathologically, the liver is colored yellow-brown and is tough and nonelastic. Histologically, the hepatic cells give the appearance of "plant-like" adenomata and contain large amounts of glycogen.

As the result of impaired glycogen, fasting hypoglycemia occurs and produces convulsive seizures, fatty liver, malnutrition, defective growth, ketosis, gluconeogenesis from protein, and negative nitrogen balance The results of excess glycogen storage in tissue are cardiomegaly and hepatosplenomegaly and impaired hepatic and cardiac function, conversion of carbohydrate to fat and obesity, disturbed muscular metabolism resulting in weakness and dyspnea, impaired leukocytic activity and infection.

ERYTHROBLASTOSIS FETALIS

The literature on the association of hepatic disease and erythroblastosis fetalis has been extensive The following hepatic conditions have been noted to occur: hemolytic jaundice, kernicterus, obstructive jaundice due to intrahepatic inspissated bile,[41, 44, 118, 101, 131] hemosiderosis,[67, 191] infantile hepatitis,[41, 90] biliary duct atresia, hepatic necrosis, hepatic fibrosis,[41, 101, 123] cirrhosis,[23, 41, 53, 102, 219] biliary cirrhosis,[43, 76, 101, 150, 219, 220] portal cirrhosis,[219] infantile or congenital cirrhosis,[67, 101, 160, 170, 220, 240] and postnecrotic cirrhosis (Fig 13) [77, 219] On the other hand, cirrhosis has been considered to be a relatively uncommon complication of this condition [76] Erythroblastosis fetalis is the result of hemolysis of erythrocytes in infants due to the presence of Rh, Hr, or ABO maternal antibodies Most frequently this condition occurs in an Rh-negative mother, producing Rh antibodies which damage fetal erythrocytes and cause a hemolytic anemia in the infant Extramedullary erythropoiesis occurs in the liver Hawksley and Lightwood in 1934 were among the first to provide evidence that in infants cirrhosis may be the result of erythroblastosis fetalis [101]

In an autopsy study of 141 cases of erythroblastosis fetalis, Craig found 10 cases of hepatic necrosis, 4 cases of hepatic necrosis and fibrosis, and 2 cases of cirrhosis [53] The latter two cases died at six and three weeks, respectively (Fig 14) Since this report, Craig believes that the two cases of cirrhosis actually represent late stages of neonatal hepatitis coincident with erythroblastosis fetalis [40] Hsia and his co-workers in 1952 studied 156 infants with prolonged obstructive jaundice [114, 116] They found 23 cases (15 per cent) of obstructive jaundice due to inspissated bile as the result of erythroblastosis fetalis Gerrard in 1952 reviewed 79 children with ery-

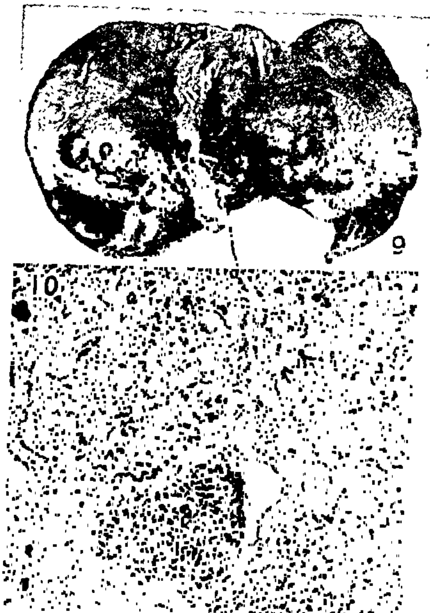


FIG 14 Specimen of liver with cirrhosis in erythroblastosis fetalis Weight of liver and spleen together 189 gm (normal weight 139 gm), dark green nodular surface tinged with brown Eventually the senior author reconsidered this case to represent a probable sequellae of neonatal hepatitis (Courtesy, Craig, J M, et al—Arch Path—June, 1950)

throblastosis fetalis, 11 of whom had hepatic dysfunction and none had cirrhosis[76] Henderson in 1942 reported a series of cases of erythroblastosis fetalis and classified them into four categories first, hemolytic anemia was found in 7 cases; second, there were 17 cases of icterus gravis in which 7 cases were cirrhosis; third, 8 cases of hydrops fetalis were reported, in which there was 1 case of cirrhosis, and last, 1 cases were characterized by a macerated fetus, cirrhosis and splenomegaly, probably the result of hydramnios[102] Keller and Nute studied 10 cases of cirrhosis in children, 5 of which were considered due to erythroblastosis fetalis[127] Consequently, cirrhosis complicating erythroblastosis fetalis is a relatively uncommon condition

It has been suggested that hepatic injury in erythroblastosis fetalis is due to extramedullary hematopoiesis, hemolytic anemia and hepatic anoxia or that hepatocellular damage is due to the direct effect of an antibody Ehrlich and Ratner suggest that there is insufficient evidence that neonatal hepatitis is viral in etiology[67] They report 2 cases of congenital cirrhosis in siblings, 1 having hematemesis They died six and one-half hours and forty-five hours after birth They believe that a relationship exists between congenital cirrhosis and iso-immunization despite the absence of Rh or ABO incompatability[41 99 170] It has been recognized by some observers that cirrhosis with parenchymal "giant cells" occurs in cases of erythroblastosis fetalis[67 102 229 230]

SICKLE CELL DISEASE

This chronic heredito-familial hemolytic anemia is almost exclusively found in the Negro race Crises of acute abdominal pain, cholelithiasis, hepatosplenomegaly, splenic infarction, fever, ulcers of the legs, bone deformities as kyphosis, scoliosis and tower-shaped skull, jaundice and rheumatoid manifestations are the essential clinical symptoms[105] A "ground glass' and eventually a hair-on-end" appearance of the skull may be demonstrated roentgenologically Sickle cell disease in which the hemoglobin is abnormal may

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FIG 14b Same liver Marked hepatocellular necrosis, fibrosis and nodular regeneration stasis of bile and fibrosis (Mallory's hemofuchsin, X140) (Courtesy, Craig J M, *et al* – Arch Path – June, 1950)

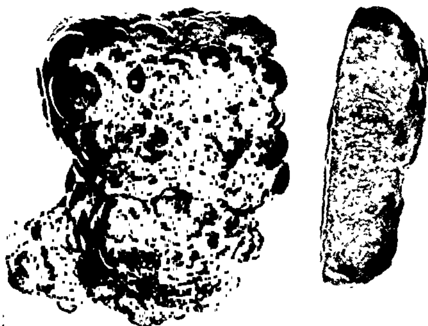


FIG 15 The superior aspects of postnecrotic cirrhosis Sickle cell disease was confirmed and considered to be a cirrhotogenic factor. (Courtesy, Song, Y. S – Arch Path—1955)

be associated with a high incidence of hepatic damage Instances of acute and chronic hepatitis, focal hepatic necrosis, hepatic fibrosis, hemochromatosis, hepatic hemosiderosis, subacute atrophy of the liver, and cirrhosis have been described in patients with sickle cell disease [20, 44, 91, 97, 125, 132, 173, 179, 195, 198, 205] In 1955 Yo Seup Song reviewed the literature on sickle cell disease and described postnecrotic cirrhosis in a fifteen year old Negro with sickle cell disease (Fig 15).[195] Death was due to ruptured esophageal varices. Rich in 1928 found 1 case of cirrhosis in 62 cases of sickle cell disease and 5,000 necropsies.[173] In 1957 Song reported 9 cases of postnecrotic cirrhosis among 31 cases of sickle cell anemia at necropsy.[196] Transfusional hemochromatosis has been described in patients with this condition. Bogoch's case was a twenty-five year old Negress who had received multiple transfusions of blood over a period of six years. This was considered to be transfusional hemochromatosis

despite absence of the classical symptoms, known rarity of the disease in women and in the Negro race, and questionable hepatic histologic criteria of hemochromatosis.[20] Many of these cases of transfusional hemochromatosis are irrefutable transfusional hemosiderosis. Portal cirrhosis has been reported in several cases with sickle cell disease.[20,91,132] Infectious or serum hepatitis, fatty infiltration of the liver due to hepatic anoxia, hepatic parenchymal ischemia and necrosis as the result of intrasinusoidal obstruction by clumps of erythrocytes, agglutinative thrombi of the hepatic capillaries, "hepatotoxin" associated with sickle cell crises, chronic passive congestion, stored iron due to multiple transfusions of blood or hemolytic anemia, and malnutrition have been considered as pathogenetic factors in producing hepatic injury in patients with sickle cell disease.[20,35,135,196]

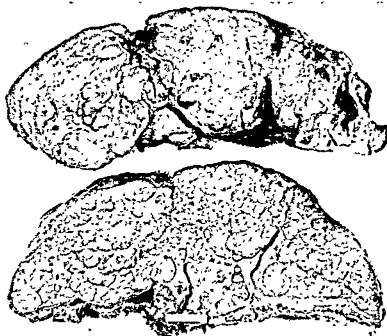


FIG. 16a. Gross lateral and sagittal sections of a liver with cirrhosis in fibrocystic disease of the pancreas. Grossly, this specimen suggests postnecrotic cirrhosis. (Courtesy, di Sant'Agnese, P. A., and Blanc, W. A.—Pediatrics—Sept. 1956.)



Fig. 16b Serial histological sections of the same liver Two large foci of regenerative nodules coalesce and four lobules are encircled by fibrous strands extending from the main foci (Courtesy, di Sant'Agnese, P A, and Blanc, W. A —Pediatrics—Sept, 1956)

FIBROCYSTIC DISEASE OF THE PANCREAS

Fibrocystic disease of the pancreas or mucoviscidosis is a hereditary disease of infants and children affecting the exocrine glands such as the sweat, salivary, and pancreatic glands and the liver and lungs [7, 70]. Di Sant' Agnese has stated that this general glandular disorder in infants and children accounts for virtually all cases of pancreatic deficiency, the majority of chronic (nontuberculous) pulmonary disease, and one-third of children with cirrhosis of the liver and portal hypertension [58]. Steatorrhea due to a deficiency of pancreatic enzymes, malnutrition, meconium ileus, bronchiectasis, lung abscess, and bronchopneumonia are observed in patients with fibrocystic disease of the pancreas. Salt depletion in hot weather due to abnormal increased excretion of sweat and vomiting may produce a hypochloremic, hyponatremic and possibly hypokaliemic alkalosis and dehydration [7, 47, 60, 81, 190].

It has been suggested that the pathogenesis of hepatic injury and fibrocystic disease is similar to the experimental production of fatty liver and cirrhosis in pancreatectomized animals sustained on an adequate diet and insulin [5, 34]. The association of steatorrhea, protein malnutrition with the production of fatty livers and cirrhosis has been recognized in kwashiorkor. Cirrhosis in this condition has been suggested to be the result of malnutrition, cholangitis, and chronic pulmonary disease [59, 59, 220]. Inspissation in the intrahepatic bile ducts of a thick eosinophilic mucoprotein in this condition has been reported to account for obstruction and dilatation of these bile ducts, hepatic fibrosis and atrophy, and cirrhosis [17, 19, 42, 71, 72]. Consequently, fibrocystic disease of the pancreas must be considered a disease with systemic manifestations. Among these are various types of hepatic injury. Fatty infiltration of the liver, focal necrosis, hepatic fibrosis, portal, postnecrotic, and biliary cirrhosis have been described in this condition. These hepatic

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FIG. 16c. Subsequent histological evidence of cirrhosis. Large strands of fibrous connective tissue with proliferated bile ducts encircle irregular areas formed by pseudo-lobules (*lower left*) or by groups of partially preserved lobules (*upper left* and *lower right*). (Courtesy, di Sant'Agnese, P. A., and Blanc, W. A.—Pediatrics—Sept., 1956.)

manifestations of fibrocystic disease of the pancreas may predominate the clinical picture.

Poppenpohl in 1909 described 22 cases of atrophic cirrhosis and 2 cases of hypertrophic cirrhosis associated with intralobular sclerosis of the pancreas.[160] De Lange in 1927 described an infant with pancreatic fibrosis and cirrhosis [34] Anderson in 1938 described 49

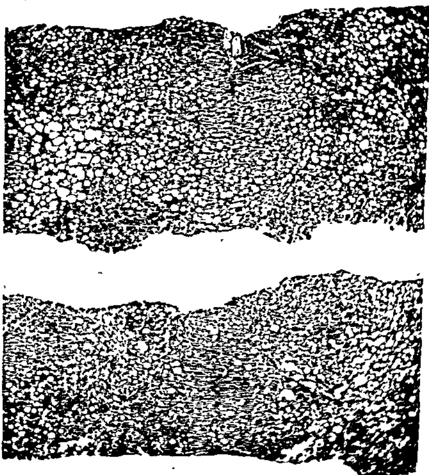


FIG 16d Histological specimens of liver obtained by needle biopsy of an enlarged liver in a child *Marked fatty infiltration was found Thereafter a diagnosis of congenital fibrocystic disease of the pancreas was established* (H & F x 60)

cases of fibrocystic disease of the pancreas in whom fatty liver was present in 19, hemosiderosis, presumably malnutritional, in 18, portal cirrhosis in 2, and biliary cirrhosis in 1.[37] Farber observed an unfamiliar type of cirrhosis in 1 out of 87 cases, and attributed this cirrhosis to obstruction of the intrahepatic bile ducts with inspissated eosinophilic material.[71] Baggenstoss and Kennedy report fatty livers in half of their 14 patients.[11] Bodian described "focal biliary fibrosis" in approximately one-fourth of 62 patients with fibrocystic disease of the pancreas.[19] Webster and Williams in 1953 reported 5 patients with multilobular cirrhosis suggesting postnecrotic cirrhosis and fibrocystic disease of the pancreas.[229] Subsequently, Craig, Gellis and Hsia observed at necropsy 7 children with obstructive biliary cirrhosis out of 160 cases with this condition.[42] Postnecrotic cirrhosis has been reported in this disease.[148,181] Di Sant'Agnese and Blanc described a distinctive type of multilobular biliary cirrhosis with portal hypertension in 7 out of 325 patients observed with fibrocystic disease of the pancreas at the Babies Hospital in New York between 1935 and 1955.[54] Four boys and three girls between the ages of four and ten years were studied. All had generalized obstructive emphysema, chronic bronchopneumonia, pancreatic exocrine deficiency, increased concentrations of sodium and chloride in the sweat, hepatosplenomegaly and clinical evidences of portal hypertension. Jaundice was absent, and there was a notable lack of consistency in the hepatic function tests. Surgical shunting procedures were performed on 4 cases.

Di Sant'Agnese and Blanc have described the pathological sequence of events in the liver involved in fibrocystic disease of the liver (Fig. 16).[54] The initial lesion is a focal biliary cirrhosis with concentrations of amorphous eosinophilic material plugging the bile ductules, inflammatory reaction and absence of marked bile stasis in the surrounding parenchyma. The concretions are located initially at the junction of the cholangioles and bile ducts and in the smaller bile ducts at the periphery of the portal spaces. These concretions may induce an acute and chronic pericholangitis. Eventually, the inflammatory foci coalesce with extension of fibrosis and atrophy of the intervening hepatic parenchyma to form a multilobular biliary cirrhosis with concretions. Groups of lobules are

encircled by fibrous connective tissue which destroy the normal parenchymal architecture Large irregular regenerative nodules are formed, simulating a postnecrotic type of cirrhosis Bile stasis is either absent or moderate Once this phase of the disease occurs, there results marked hepatosplenomegaly, and ascites and rupture *of esophageal varices becomes clinically apparent.*

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Chapter 13

CIRRHOSIS ASSOCIATED WITH OTHER CONDITIONS

INTRODUCTION

As THE RESULT of the use of needle biopsy of the liver and a battery of hepatic function tests, various types of hepatic injury have been detected in certain diseases and conditions other than primary disease of the liver. In this chapter the effect and relation of cirrhosis will be considered in the following disorders: (1) diseases of the endocrine glands such as thyrotoxicosis and diabetes mellitus; (2) pregnancy; (3) congestive heart disease, (4) regional enteritis, (5) chronic ulcerative colitis, (6) infectious and parasitic diseases such as brucellosis, infectious mononucleosis, and kala-azar; (7) "florid cirrhosis"; (8) chronic relapsing pancreatitis, and (9) the de Toni-Fanconi syndrome. The pathogenetic mechanism of cirrhosis in many of these clinical entities may be obscure, or may be the result of multiple factors such as a virus, bacteria, toxins, anoxia, congestion, malabsorption, malnutrition, disturbed metabolic and endocrine relationships, stress and systemic disease. The disease and conditions presented in this chapter have been selected because their association with cirrhosis constitutes either an unique complication or a significant clinical problem.

THYROTOXICOSIS

The development of hepatic damage in patients with thyrotoxicosis has been known since 1865 when Paul reported cirrhosis in a thirteen year old patient with exophthalmic goiter present for four years.[43, 211] Since then there have been numerous reports on the association and pathogenesis of hepatic disease in thyrotoxicosis. However, within the past two decades, as the result the treatment of thyrotoxicosis by goitrogenic drugs, nutritious diet, and subtotal thyroidectomy and the reduction of complications of this condition such as congestive heart failure and thyroid crisis, the incidence of hepatic injury in thyrotoxicosis is decreased.[199, 274] Two hundred forty-nine consecutive cases of thyrotoxicosis between

Medical Research Council Special Report Series, No 263, London, Her Majesty's Stationery Office, 1948.

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Fatty infiltration, centrilobular and diffuse hepatic necrosis, hepatic fibrosis, chronic localized interstitial hepatitis, serous hepatitis, chronic passive congestion and cirrhosis are the principal pathological lesions of the liver described in thyrotoxicosis [21, 43, 197, 241, 278, 282, 283] A lesion simulating portal cirrhosis was described by Warthin in a study of hepatic lesions in thyrotoxicosis [278] This consisted of a parenchymatous hepatitis with lymphocytic infiltration, increased connective tissue, and bile duct proliferation in the portal areas Trousseau in 1868 described 2 cases of "hypertrophic cirrhosis" associated with thyrotoxicosis.[268] Rossle described a particular type of cirrhosis occurring in patients with thyrotoxicosis, the pathogenesis of which was assumed to be "serous hepatitis" of toxic origin or increased cardiac output.[231, 232] He emphasized the accumulation of lymph, congestion of blood, proliferation of collagenous fibrils in the spaces of Disse, and predilection of this process for the subapsular areas of the liver Moschowitz has also described a type of

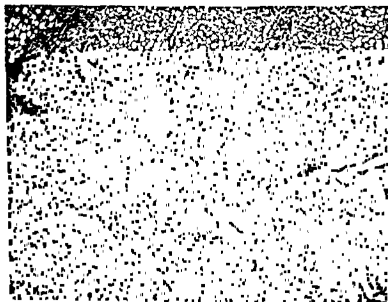


FIG 1a Histological picture of liver in a case of untreated hyperthyroidism Hepatomegaly and hepatic function tests suggestive of cirrhosis Marked fatty infiltration and portal cirrhosis (H & E, X60)

TABLE I
CLINICAL AND LABORATORY DATA OF A FORTY-SEVEN YEAR OLD MAN WITH THYROTOXICOSIS AND PORTAL CIRRHOSIS

Clinical Manifestations	Year *1949*	*1950*	*1952*
Body weight, lb.	123	149	146
Weakness	+	+	0
Nervousness	+	+	0
Perspiration	+	0	0
Tremor	+	0	0
Diarrhea	+	0	0
Palpitation	+	0	0
Dyspnea	+	0	0
Exophthalmos	+	0	0
Quadraceps weakness	+	+	+
Hepatomegaly	+	0	0
Pulse rate	5f	5f	3f
Edema	116	104	86
Jaundice	+	0	0
	+	+	0
Laboratory Data			
BMR	+65	-21	-4
Bilirubin, serum, mg./100 cc	0.21 / 1.45	0.12 / 2.26	0.4 / 1.2
BSP % Retention 45'	17	5	0
Cholesterol, plasma, mg./100 cc	294	393	—
Albumin, serum, gm./100 cc	4.0	—	4.2
Globulin, serum, gm./100 cc.		—	2.4
Cephalin flocculation, units	1+	0	0
Prothrombin time, % of normal	77	82	100
Treatment	Lugol's Solution, propylthiouracil, high protein, high caloric diet; vitamins	Subtotal Thyroidectomy	Asymptomatic Cirrhosis

1945 and 1954 were reviewed. In only one instance was there any established evidence of hepatic disease (Table I) (Fig. 1a). This patient illustrated marked clinical improvement of portal cirrhosis following successful management of thyrotoxicosis. In contrast, 116 consecutive patients with thyrotoxicosis were reviewed between 1925 and 1934 and morphological evidence of hepatic disease was found in 5 cases of which 2 cases were portal cirrhosis. One may presume hepatic damage in thyrotoxicosis is related to the duration, severity, malnutrition, and complications of this disorder. The production of liver disease in thyrotoxicosis has been considered to be due to increased cardiac output, congestive heart failure, hepatic hypoxia, reduction of hepatic glycogen, malnutrition, susceptibility to infections, and effect of thyroxin on intermediary metabolism.

to determine the incidence and type of associated hepatic disease Weller in 1930 found 22 cases of chronic interlobular parenchymatous hepatitis and no case of cirrhosis in 41 cases of thyrotoxicosis [252, 253] Habán in 1933 found cirrhosis in 38 8 per cent and fatty infiltration in 23 per cent of cases of thyrotoxicosis, and suggested that cirrhosis in this condition be named 'hepar basedowianum or cirrhosis basedowiana' [102] Beaver and Pemberton in 1933 studied the liver in 107 fatal cases of thyrotoxicosis [23] They found fatty infiltration or focal or central necrosis of the liver in 91 5 per cent of the cases atrophy in 63 6 per cent, chronic cirrhosis in 60 per cent and advanced cirrhosis in 15 per cent However in many of their cases of cirrhosis, the histological criterion of nodular regeneration was absent They noted that cirrhosis was present more frequently *in older patients having severe thyrotoxicosis of prolonged duration* The average weight of the cirrhotic livers in their series was 1,258 gm Ascites jaundice, marked elevation of the basal metabolic rate, and thyroid crises were common in this group Cameron and Karunaratne studied the morphology of the liver in 30 necropsy cases of thyrotoxicosis [43] There were 10 cases with chronic passive congestion, 5 with fatty changes with or without hepatic necrosis, 5 with atrophy and nodule formation, and 10 with cirrhosis Shaffer reported a study of hepatic damage in 24 cases of thyrotoxicosis of which fatty infiltration was found in 11 7 per cent, chronic localized interstitial hepatitis in 83 3 per cent and cirrhosis in 25 per cent (6 cases) [243] Movitt and his co-workers recently studied 13 patients with thyrotoxicosis by needle biopsy of the liver and hepatic function tests [199] As a result of their study they were unable to discover any significant hepatic lesions in uncomplicated thyrotoxicosis

DIABETES MELLITUS

There are several reports in the literature concerning the production of abnormal hepatic function tests, fatty infiltration of the liver and cirrhosis in patients with diabetes mellitus, and the effect of hepatic injury, particularly cirrhosis, conversely upon diabetes mellitus The liver is an important organ in the metabolism of carbohydrates and the homeostatic regulation of blood sugar In fact there have been two theories in regard to the specific defect in carbohydrate metabolism in diabetes mellitus One, the under-

cirrhosis pathognomonic of thyrotoxicosis similar to Rossle's description in 10 of 31 cases.[197] The regenerative nodules may be either granular or nodular This cirrhosis was regarded as the consequence of forward congestive failure as the result of increased velocity of blood flow and increased blood volume. The initial hepatic lesion is regarded as capillary congestion progressing to capillary sclerosis and fibrosis This cirrhosis arises from the smaller subdivisions of the portal spaces and is predominant in the subcapsular zone of the liver Portal cirrhosis which is assumed to be the result of malnutrition or the toxic effects of hypermetabolism has been described in several reports [11, 21, 43, 79, 98, 100, 107, 176, 213, 222, 241] Abnormalities in hepatic function tests, especially the galactose-tolerance and bromsulfalein-retention tests occur in patients with thyrotoxicosis, which may be corrected by thyroidectomy [6, 18, 33, 34, 39, 106, 164, 167, 170, 185, 291]

Several large necropsy series of thyrotoxicosis have been studied

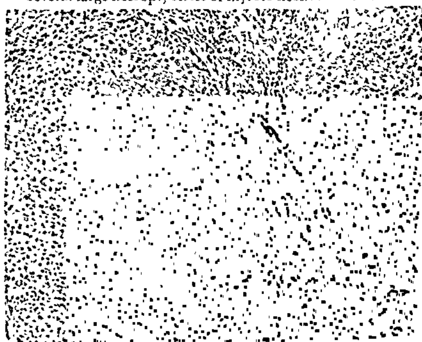


Fig 1b Histological picture of the liver in a patient with diabetes mellitus and portal cirrhosis with minimal fatty infiltration Death was due to hepatic insufficiency (H & E, X60)

ing's disease, obesity, regulation, severity and complications of diabetes mellitus, congestive heart failure, infectious and serum hepatitis and "florid cirrhosis" which may occur in patients with diabetes mellitus. In patients with cirrhosis and diabetes mellitus, correct management of the diabetes may also produce improvement in hepatic function. Cirrhosis, on the other hand, usually intensifies diabetes mellitus and treatment of the hepatic dysfunction may improve the diabetes. It has been reported that cirrhosis actually ameliorates diabetes mellitus.[32]

PREGNANCY

Various studies have shown that pregnancy imposes a burden upon the liver of the pregnant woman in the form of abnormalities of hepatic function tests, jaundice, and an increased incidence of hepatic diseases.[94, 268, 287a] Jaundice and fatty infiltration and centrilobular necrosis of the liver may occur as the result of hyperemesis gravidarum. Alterations in hepatic function tests and infrequently jaundice and hemorrhage necrosis occur in eclampsia of pregnancy.[103, 128, 203, 281] The significance of infectious hepatitis complicating pregnancy is not the increased incidence but actually the maternal and infant mortality, the frequency of fatal acute hepatic necrosis, chronic hepatitis, and postnecrotic cirrhosis in the mother, spontaneous abortions, particularly in the third trimester, and the occurrence of fetal anomalies.[23, 73, 94, 122, 145, 166, 175, 177, 208, 210, 234, 288, 297, 298] The syndrome of "jaundice in late pregnancy" has been thoroughly reviewed by Thorling.[264] This condition is characterized by abdominal distress, lassitude, pruritus, jaundice, mild to moderate clinical course, recurrence in succeeding pregnancies and premature labor. Acute fatty infiltration of the liver may occur in pregnant mothers and may be fatal.[203, 243]

Pregnancy occurs rarely in patients with cirrhosis.[41, 169, 237, 245, 264, 287a] This implies infrequent conception by the cirrhotic mother. The mortality of the pregnant cirrhotic patient has been reported to be approximately 26 per cent.[247a] Slater reported a case of a white female with postnecrotic cirrhosis of at least four years' duration who became pregnant at the age of twenty-nine.[245] The pregnancy was uneventful, resulting in an uncomplicated delivery of a healthy

utilization concept of Mering and Minkowski in 1899, stated that the peripheral utilization of glucose is impaired and hepatic glycogenolysis is normal.[171] The other, the overproduction concept postulated by van Noorden and Isaac in 1929 and Soskin in 1941 stated that in diabetes mellitus there is unrestrained production of hepatic glucose resulting in hyperglycemia and that the peripheral utilization of glucose is normal[248-252] Furthermore, another hormone, glucogen, the pancreatic hyperglycemic-glycogenolytic factor, has recently been found to produce hepatic glycogenolysis [39,40,45]

It is obvious that in hepatic disease, diabetes mellitus or their combinations may interfere with glyconeogenesis, glycogenesis, glycogenolysis, and the amount of stored hepatic glycogen It is well known that in patients with diabetes mellitus, abnormalities, particularly in the bromsulphalein retention, appear related to the severity and complications of diabetes mellitus [93,101,134,162,199,234] Abnormal hepatic flocculation tests occur in approximately 20 per cent of diabetic patients Hyperglycemia and abnormal glucose tolerance tests have been noted in patients with liver disease which revert to normal after successful therapy.[19,20,44,115,161,162,249,252,259,254] Sherlock has called "hepatic sensitive" those diabetics in whom the intravenous administration of insulin results in a marked hypoglycemia, and "hepatic insensitive diabetes" those in whom only a slight decrease in blood glucose if any occurs[243] She has noted fatty infiltration of the liver in the "hepatic insensitive" diabetics

Enlargement of the liver, fatty infiltration of the liver, increased cytoplasmic vacuolated glycogen, hemosiderosis and cirrhosis have been reported as complications of diabetes mellitus (Fig 1b) [93,111,217,227,276,286,294] Fatty liver has been noted in nearly 20 per cent of diabetic patients studied at necropsy[217,227,276] While the transition from a fatty liver to portal cirrhosis has been recognized in diabetics, in most series the incidence of cirrhosis in diabetes mellitus is not increased.[15,59,138,139,223,247] Other series, conversely, report a high incidence of cirrhosis in patients with diabetes mellitus ranging from 12.7 per cent of Schleusner to 16 3 per cent of Jaques.[131,240] The descrepancy of these statistics may well be explained by the presence of alcoholism, malnutrition, anemia, pancreatitis, Cush-

ing's disease, obesity, regulation, severity and complications of diabetes mellitus, congestive heart failure, infectious and serum hepatitis and "florid cirrhosis" which may occur in patients with diabetes mellitus In patients with cirrhosis and diabetes mellitus, correct management of the diabetes may also produce improvement in hepatic function. Cirrhosis, on the other hand, usually intensifies diabetes mellitus and treatment of the hepatic dysfunction may improve the diabetes It has been reported that cirrhosis actually ameliorates diabetes mellitus[32]

PREGNANCY

Various studies have shown that pregnancy imposes a burden upon the liver of the pregnant woman in the form of abnormalities of hepatic function tests, jaundice, and an increased incidence of hepatic diseases[94 208 287a] Jaundice and fatty infiltration and centrilobular necrosis of the liver may occur as the result of hyperemesis gravidarum Alterations in hepatic function tests and infrequently jaundice and hemorrhage necrosis occur in eclampsia of pregnancy[103 129 203 281] The significance of infectious hepatitis complicating pregnancy is not the increased incidence but actually the maternal and infant mortality, the frequency of fatal acute hepatic necrosis, chronic hepatitis, and postnecrotic cirrhosis in the mother, spontaneous abortions, particularly in the third trimester, and the occurrence of fetal anomalies[23,73 94 122,146,166 173,177,208 210 234 264 295 ,296] The syndrome of "jaundice in late pregnancy" has been thoroughly reviewed by Thorling[264] This condition is characterized by abdominal distress, lassitude, pruritus, jaundice, mild to moderate clinical course, recurrence in succeeding pregnancies and premature labor Acute fatty infiltration of the liver may occur in pregnant mothers and may be fatal[205,283]

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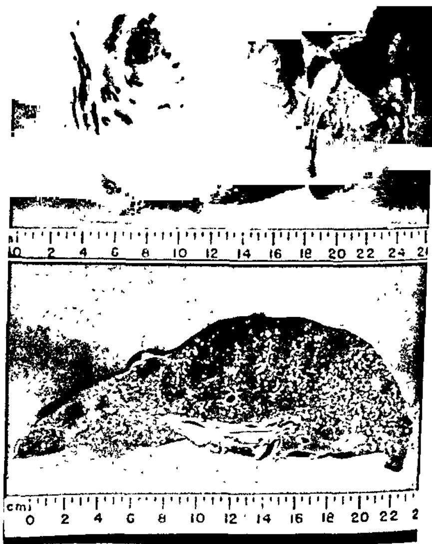


FIG. 2a Superior surface of the liver of subacute viral hepatitis in a stage of developing into postnecrotic cirrhosis, patient presumably contracted infectious hepatitis and died in the third trimester of pregnancy in hepatic coma twenty five days following the spontaneous abortion of an icteric, premature, well developed infant Among the significant findings at necropsy were marked ascites, edema, deeply icteric organs, hydrothorax, hemorrhagic gastroenteritis,

infant. However, one year later the patient died as the result of cirrhosis. Four more similar cases of pregnancies in cirrhotics have been reported.[41, 237, 264] Apparently, if cirrhosis is latent or uncomplicated, the chances of successful pregnancy and delivery are not entirely hopeless

That pregnancy adversely affects the cirrhotic is illustrated by the following case Mack and his associates have reported 3 patients of pregnancy complicated by cirrhosis.[169] One of their cases, a twenty-eight year old primipara with primary biliary cirrhosis suffered from jaundice, abdominal pain, vaginal bleeding, and edema after the fifth month of gestation. Pregnancy was terminated by caesarean section in the thirty second week She recovered during the post-partum period A patient with pregnancy and cirrhosis was recently studied. During the last trimester there was marked subjective and objective improvement in the status of the patient's liver disease, improvement of her liver function tests and subsidence of jaundice. However, similar to Slater's case, the patient died several months after delivery It would appear that possibly the sudden removal of an auxiliary hypertrophied fetal liver resulted in hepatic insufficiency in the post-partum period Recently, a thirty-six year old female was observed with infectious hepatitis in the seventh month of gestation She aborted spontaneously after having been in hepatic coma for eleven days she then survived for an additional eighteen days. Necropsy examination disclosed early postnecrotic cirrhosis (Fig 2a, 2b, 2c). The infant had marked hepatomegaly and jaundice at birth which subsided within several weeks, and no hepatic sequelae were noted

CONGESTIVE HEART FAILURE

Since Becquerel in 1840 stated that half of the cases of cirrhosis he observed were due to congestive heart failure, the relationship of these two conditions has been controversial.[151] Such *confusion*

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generalized cutaneous and visceral petichiae, hepatosplenomegaly, generalized postthrombotic (?) necrosis of right frontal lobe of brain and "bile nephrosis", weight of liver 2,250 gm multiple rudimentary regenerative nodules firm consistency, dark greenish brown color

FIG 2b Sagittal section of specimen in Figure 2a

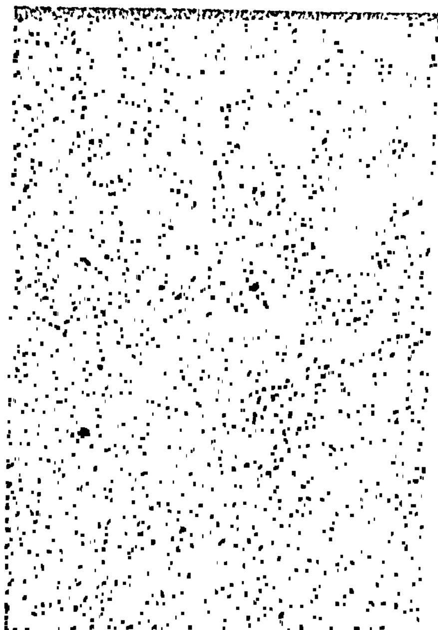


Fig 2c Histological findings of a liver with gross morphological evidence of postnecrotic cirrhosis Death due to an exsanguinating gastrointestinal hemorrhage, an aneurysm between common bile duct and right portal vein Esophago-

has been the result of the liberal morphological interpretation of the term "cirrhosis" and the frequency of abnormalities in hepatic function tests, occurrence of jaundice, abdominal pain, nausea, vomiting, hepatosplenomegaly, ascites, and edema in patients with right heart failure. Marked abnormalities in hepatic flocculation tests may occur in patients with congestive heart failure.[illegible] In fact, the clinical findings observed in patients with congestive heart failure due to chronic constrictive pericarditis and tricuspid valvular insufficiency or stenosis may simulate those of cirrhosis. Congestive heart failure initially produces distention of the sinusoids, centrilobular congestion, and atrophy of hepatic cells in the central areas of the hepatic lobules (Fig. [illegible]).[illegible] The pathogenesis of these hepatic lesions has been stated to be reduction in hepatic blood flow, deficient oxygen supply to the liver, associated anemia and nutritional deficiency, and mechanical compression of the centrilobular hepatic area.[illegible] Fatty infiltration of the liver and atrophy and necrosis of the central hepatic cells occurs in progressive and long standing congestive heart failure. When advanced, it explains the clinical jaundice in this condition in the absence of concomitant pulmonary infarction. Coalescence of the necrotic centrilobular areas may result in the formation of pseudolobule formation with the portal areas of the liver occupying the center of the pseudolobules surrounded by surviving hepatic cells. Farrar has described progressive hepatic lesions in congestive heart failure to be condensation of the reticulum in the degenerated central areas of the hepatic lobule, marked thickening of walls of the central veins and hepatic veins, and, ultimately, fibrosis of the liver with active fibroblastic proliferation.[illegible] Some observers regard this state as cardiac cirrhosis, even though the morphological findings are not uniform.[illegible] This advanced stage has been described as cardiac fibrosis.[illegible]

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gastric balloon tamponade had been used. Specimen shows practically no evidence of cirrhosis. There is marked hepatocellular necrosis, moderate stasis of bile, and such a small amount of stroma, all of which shed questionable light on the gross morphological evidence of postnecrotic cirrhosis. However, it was felt that this section served as an example never to diagnose histologically postnecrotic cirrhosis with certainty. (H & E, X[illegible].)

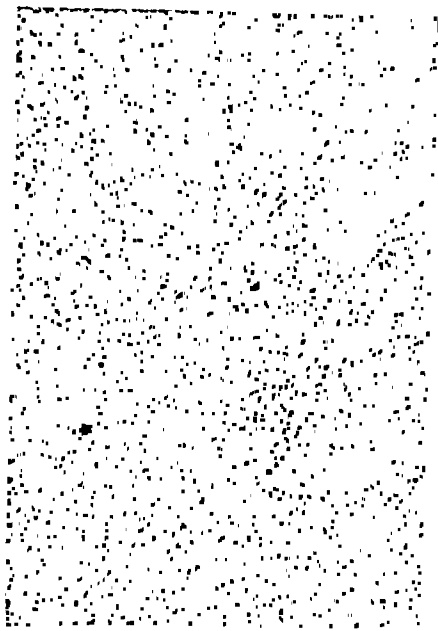


Fig. 8[illegible]. Histological findings of a [illegible] ence of

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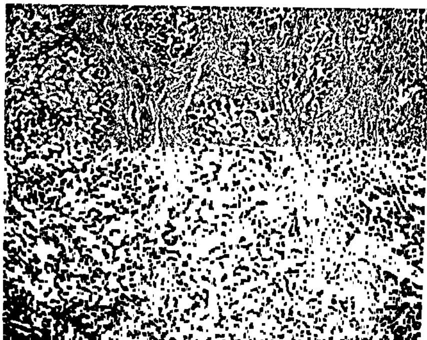


FIG 3. Histological specimen of a liver from chronic congestive heart failure due to chronic rheumatic endocarditis with mitral insufficiency, centrilobular necrosis, chronic passive congestion, and central fibrosis No histological evidence was found of cirrhosis (H & E, X80)

[95,98,113,114,157,159,180,271] Others have considered cardiac cirrhosis as either nonexistent or rare [2,82,135,181,186,220,231,232,273] It has been reported that hepatic fibrosis in congestive heart failure is portal rather than central [8,102,110,141] If nodular regeneration and porta-hepatic venous anastomoses are histological criteria of cirrhosis, and, if one excludes the possibility of possible associated cirrhotogenic conditions such as malnutrition or hepatitis, then the association of congestive heart failure and cirrhosis occurs infrequently.

Sherlock has shown that the severity of these histological findings of the liver depends on the duration and recurrence of congestive heart failure and is more commonly noted in cases of mitral stenosis, tricuspid insufficiency or stenosis and chronic constrictive pericarditis.[242] In some of her patients with congestive heart

failure, nodular regeneration of the liver was demonstrated. She prefers to employ the term "cardiac cirrhosis" with only morphological implications and little or no clinical significance. It is best to avoid use of the term "cardiac cirrhosis" unless there is histological confirmation. Esophageal varices, abnormalities in hepatic flocculation tests, and hyperglobulinemia have been observed rarely in cases of congestive heart failure, particularly chronic pericarditis and tricuspid valvular lesions with histological confirmation of cirrhosis.

REGIONAL ENTERITIS

The infrequency of significant hepatic lesions in patients with regional enteritis is notably absent in the reports of large series of cases of regional enteritis.[33, 62, 64, 172, 253, 270, 277] This seems unusual because this chronic granulomatous condition, which may involve all or part of the small and large intestine, has common systemic complications. It may be complicated by intestinal malabsorption, inanition, malnutrition, avitaminosis, negative nitrogen balance, shock, intestinal obstruction, hemorrhage, fever, or infection in which treatment is prolonged and often consisting of broad-spectrum antibiotic or steroid therapy, extensive intestinal resection, or multiple transfusions of plasma or blood. These factors may induce or aggravate hepatic damage and are prevalent in a similar condition, chronic ulcerative colitis, which is associated commonly with hepatic disease. Spellberg has observed fatty infiltration of the liver and nutritional cirrhosis at necropsy in several patients with regional enteritis.[253] Furthermore, needle biopsy of the liver in several of his cases of regional enteritis disclosed fatty infiltration and focal hepatitis. Patients have been observed with ileojejunitis and cirrhosis.[211] Regional enteritis, and hepatic granulomas, pylephlebitis and multiple hepatic abscesses have been published as case reports.[51, 63, 64, 130, 131, 246, 263] Chapin and his associates studied the visceral changes at necropsy in 39 cases of regional enteritis at the Mayo Clinic and found that the liver was involved more frequently pathologically than any organ other than the primary lesion.[49] The hepatic lesions in their series were fatty infiltration in 20 cases, focal necrosis in 14, chronic passive congestion in 11, perihepatitis

in 5, cirrhosis in 3, healed hepatic tubercle in 3, and acute infarction, centrilobular necrosis and hepatic amyloidosis in 2 cases each, and hepatic granuloma in 1 case In a separate investigation, hepatic function tests and needle biopsy of the liver were performed in 20 consecutive living patients with established regional enteritis[131] Histologically, the liver was normal in 17 instances There were 2 patients with regional ileitis and 1 in whom the disease involved the entire small intestine and the histological examination of the liver disclosed minimal to moderate fatty infiltration The duration of symptoms in these 3 cases averaged four years The results of the hepatic function tests were essentially normal, other than the bromsulphalein retention of 10 per cent and the serum albumen-globulin value of 2.4/2 2 gm /100 cc. in a case of regional enteritis involving the entire small intestine

There are certain important conditions to explain the relative infrequency of various types of hepatic disease including cirrhosis in patients with regional enteritis in comparison to those with chronic ulcerative colitis Rectal hemorrhages are infrequent in patients with regional enteritis and, consequently, there is a diminished incidence of serum hepatitis as the result of transfusions of blood or plasma and of hemorrhagic shock, which results in diminished hepatic blood flow and hepatic anoxic injury. Ordinarily, regional enteritis is not associated with extensive secondary bacterial infection of the involved intestine, and the liver filters less bacteria which might be hepatotoxic. Because the medical treatment of regional enteritis is generally unsuccessful, this disease is treated more readily by resection of the involved intestine than is chronic ulcerative colitis in which prolonged medical treatment is usually advocated. Fourteen of the twenty patients with regional enteritis had primary intestinal resection and had had recurrent enteritis at the time of needle biopsy of the liver. One might assume that resection of the involved intestinal segment would reduce any hepatic complications. Regional enteritis is considered a granulomatous intestinal disease with less frequent systemic complications in contrast to chronic ulcerative colitis in which the complications are protean Actually, the association of significant parenchymal hepatic disease in granulomatous disease is uncommon.

CHRONIC ULCERATIVE COLITIS

Only within recent years has hepatic disease been reported as a major complication of chronic ulcerative colitis. In 1919 Logan reported the finding at necropsy of chronic ulcerative colitis in 13 cases, in 10 of which there was infiltration of the liver with fat and in 1 there was cirrhosis.[165] In 1929 Bargen studied 693 cases of chronic ulcerative colitis and found 1 case of Banti's syndrome with biliary cirrhosis and another case of juvenile cirrhosis.[16]

Subsequently, clinical and pathological case reports and a large series of patients with chronic ulcerative colitis described clinical, biochemical, and morphological evidence of hepatic lesions obtained at necropsy or by needle biopsy of the liver in living patients. These studies disclosed that fatty infiltration of the liver, hepatitis, hepatic necrosis, multiple hepatic abscesses, hepatic amyloidosis, and cirrhosis of portal, biliary, and postnecrotic types were significant hepatic lesions.[17 42 62 132 133 140 152 153 160 174 196 226 277] Lupus erythematosus and portal cirrhosis have been described in pa-



Fig. 4a Histological specimen showing severe necrosis of the liver. Needle biopsy of the liver, acute fulminating chronic ulcerative colitis with hepatomegaly. Death due to hepatic coma (H & E, X100) (Courtesy, Kleckner, M. S., Jr., Stauffer, M. H., Bargen, J. A., and Dockerty, M. B.—Gastroenterology—September, 1952.)

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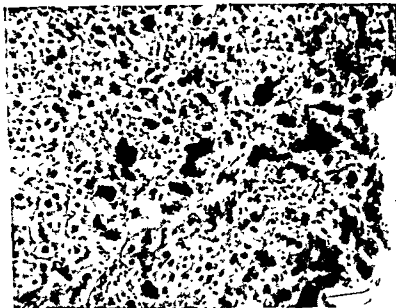


FIG 4c Histological specimen showing marked acute hepatitis, hepatocellular degeneration some regenerative hepatic cells "balloon-cells", stasis of bile, parenchymal infiltration of inflammatory cells Needle biopsy of the liver Chronic ulcerative colitis with acute infectious (?) hepatitis (H & E X100) (Courtesy, Kleckner, M S Jr, Stauffer, M H, Bargen, J A, and Dockerty, M B—Gastroenterology—September, 1952)

of hepatic disease [285a] Peritoneoscopy was the diagnostic procedure in 4 cases of cirrhosis These authors emphasized nutritional deficiency and chronic ulcerative colitis in the development of cirrhosis, although general toxemia and loss of large amounts of protein in the rectal discharges could contribute significantly to the development of a deficiency state Jones, Baggenstoss, and Bargen studied the liver obtained at necropsy in 91 cases of chronic ulcerative colitis encountered at the Mayo Clinic [133] Fatty infiltration of the liver was present in a moderate to severe degree in 47 cases (52 per cent) Cirrhosis was observed in 3 cases, and fibrosis, pericholangitis, hepatic necrosis, metastatic carcinoma, and intrahepatic thrombosis occurred occasionally Abnormal results of hepatic

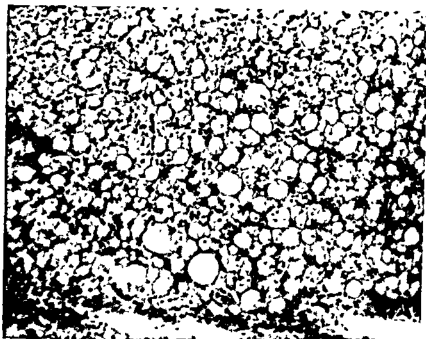


FIG 4b Histological specimen showing marked infiltration of the liver Needle biopsy of the liver, chronic ulcerative colitis for three years and moderate emaciation (H & E, X100) (Courtesy, Kleckner, M S, Jr, Stauffer, M H, Bargen, J A, and Dockerty, M B —Gastroenterology—September, 1952)

tients with chronic ulcerative colitis [31,154] Ross and Swarts reviewed 150 unselected cases of chronic ulcerative colitis and found no gross clinical evidence of hepatic disease [230] However, in 20 specially studied cases of chronic ulcerative colitis in which necropsy was performed, the most significant finding relevant to hepatic damage was hypoproteinemia. Pollard and Block, on the other hand, were able to demonstrate hepatic insufficiency in half of 70 cases of chronic ulcerative colitis.[217] In 11 of 17 cases studied at necropsy, there was evidence of hepatic lesions. Cirrhosis was present in 2 instances and fatty infiltration occurred as the commonest lesion These authors suggested that malnutrition and toxemia or both were responsible for insufficiency in this condition Among 151 patients with chronic ulcerative colitis, Tumen, Monaghan, and Jobb encountered 5 with cirrhosis, 4 of whom had clinical evidence

able degrees of fatty infiltration of the liver were observed in 11 of 16 cases of acute or chronic ulcerative colitis. Severe fatty infiltration was observed in only 1 of 13 cases of chronic ulcerative colitis in which needle biopsy of the liver was secured at laparotomy. Kimmelstiel, Large and Verner examined the livers in 93 cases of chronic ulcerative colitis at necropsy. They found the incidence of hepatic lesions in this condition as compared with a controlled series of 1,000 necropsies to be 10 per cent and there was clinical evidence of hepatic disease in approximately 10 per cent of the cases.[108] Fatty infiltration was present in 14 cases, interlobular hepatitis in 9 cases, hepatic necrosis in 8 cases, inflammatory foci in 5 cases, multiple bile casts and pseudolobulation in 2 cases each, and cirrhosis in 1 case.

Thirty two selected living patients with chronic ulcerative colitis were studied to determine the presence of hepatic disease clinically by hepatic function tests and by needle biopsy of the liver (Tables II, III).[152] Five patients had no morphological nor clinical evidence of hepatic disease. The histological findings were normal in 5 cases, fatty infiltration in 9 cases, chronic pericholangitis in 3 cases, cirrhosis in 6 cases, chronic pericholangitis with stasis of bile in 3 cases, metastatic carcinoma in 3 cases, and acute massive necrosis in 1 case (Figs. 4a, 4b, 4c, 4d). Cirrhosis was observed particularly in young adults who had had chronic ulcerative colitis from one to sixteen years. There was one patient with latent portal cirrhosis, one with "intestinal infantilism," and one with portal cirrhosis and hypersplenism (Fig. 5a, 5b). The clinical picture in 3 patients was cholangiolitic hepatitis. Postnecrotic cirrhosis was the clinical diagnosis in 3 patients with chronic ulcerative colitis. Because a small specimen of hepatic tissue was obtained by needle biopsy this diagnosis could not be verified histologically. Two patients with cirrhosis had antecedent jaundice and a cirrhotic sequela of infectious hepatitis was suspected. Abnormalities of hepatic function tests were common, particularly bromsulfalein dye retention and hypoalbumenemia. Abnormal hepatic flocculation tests, hyperglobulinemia, and elevated serum bilirubin were observed in patients with inflammatory lesions of the liver and cirrhosis. No correlation could be made between the hepatic lesion noted and the duration and ac-

function tests in cases of chronic ulcerative colitis were noted, but often were transient. These authors stated that fatty infiltration of the liver and possibly cirrhosis were probably related to malnutrition, toxemia, and the debilitating effects of chronic ulcerative colitis. Warren and Sommers studied data on 120 surgical cases of chronic ulcerative colitis and on 60 cases in which necropsy was performed.[77] Hepatic necrosis and cirrhosis were complications in 3 per cent and 2 per cent of the cases of chronic ulcerative colitis respectively. Fatty liver was found in 33 of 60 necropsies. The association of hepatic disease and chronic ulcerative colitis has been studied by Hoffbauer, and his co-workers.[119] They reviewed 270 cases of chronic ulcerative colitis. Cirrhosis of the liver was observed in 10 patients with chronic ulcerative colitis, 4 of whom had malignant degeneration of the involved portion of the colon. Vari-

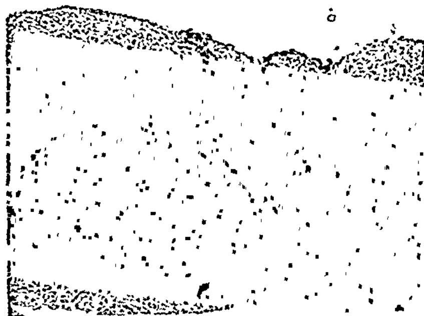


FIG. 4d. Histological specimen showing portal cirrhosis. Needle biopsy of liver: chronic ulcerative colitis for six years. Minimal hepatosplenomegaly and hepatic symptoms. (H & E, X60). (Courtesy, Kleckner, M. S., Jr., Stauffer, M. H., Bargen, J. A., and Dockerty, M. B.—Gastroenterology—September 1952)

able degrees of fatty infiltration of the liver were observed in 11 of 16 cases of acute or chronic ulcerative colitis. Severe fatty infiltration was observed in only 1 of 13 cases of chronic ulcerative colitis in which needle biopsy of the liver was secured at laparotomy. Kimmelstiel, Large and Verner examined the livers in 93 cases of chronic ulcerative colitis at necropsy. They found the incidence of hepatic lesions in this condition as compared with a controlled series of 1,000 necropsies to be 10 per cent and there was clinical evidence of hepatic disease in approximately 10 per cent of the cases.[115] Fatty infiltration was present in 11 cases, interlobular hepatitis in 9 cases, hepatic necrosis in 8 cases, inflammatory foci in 5 cases, multiple bile casts and pseudolobulation in 2 cases each, and cirrhosis in 1 case.

Thirty two selected living patients with chronic ulcerative colitis were studied to determine the presence of hepatic disease clinically, by hepatic function tests, and by needle biopsy of the liver (Tables II, III).[113] Five patients had no morphological nor clinical evidence of hepatic disease. The histological findings were normal in 5 cases, fatty infiltration in 9 cases, chronic pericholangitis in 3 cases, cirrhosis in 6 cases, chronic pericholangitis with stasis of bile in 3 cases, metastatic carcinoma in 3 cases, and acute massive necrosis in 1 case (Figs. 1a, 1b, 1c, 1d). Cirrhosis was observed particularly in young adults who had had chronic ulcerative colitis from one to sixteen years. There was one patient with latent portal cirrhosis, one with "intestinal infantilism," and one with portal cirrhosis and hypersplenism (Fig. 5a, 5b). The clinical picture in 3 patients was cholangiolitic hepatitis. Postnecrotic cirrhosis was the clinical diagnosis in 3 patients with chronic ulcerative colitis. Because a small specimen of hepatic tissue was obtained by needle biopsy this diagnosis could not be verified histologically. Two patients with cirrhosis had antecedent jaundice and a cirrhotic sequela of infectious hepatitis was suspected. Abnormalities of hepatic function tests were common, particularly bromsulfalein dye retention and hypoalbumenemia. Abnormal hepatic flocculation tests, hyperglobulinemia, and elevated serum bilirubin were observed in patients with inflammatory lesions of the liver and cirrhosis. No correlation could be made between the hepatic lesion noted and the duration and ac-

function tests in cases of chronic ulcerative colitis were noted, but often were transient These authors stated that fatty infiltration of the liver and possibly cirrhosis were probably related to malnutrition, toxemia, and the debilitating effects of chronic ulcerative colitis Warren and Sommers studied data on 120 surgical cases of chronic ulcerative colitis and on 60 cases in which necropsy was performed [277] Hepatic necrosis and cirrhosis were complications in 3 per cent and 2 per cent of the cases of chronic ulcerative colitis respectively Fatty liver was found in 33 of 60 necropsies The association of hepatic disease and chronic ulcerative colitis has been studied by Hoffbauer, and his co-workers [118] They reviewed 270 cases of chronic ulcerative colitis Cirrhosis of the liver was observed in 10 patients with chronic ulcerative colitis, 4 of whom had malignant degeneration of the involved portion of the colon Vari-



Fig 4d Histological specimen ... liver, chronic ulcerative colitis for six years ... hepatic symptoms (H & E, X60) (Courtesy, Kleckner, M S, Jr, ... H, Bargen, J A, and Dockerty, M B—Gastroenterology—September, 1952)

able degrees of fatty infiltration of the liver were observed in 11 of 16 cases of acute or chronic ulcerative colitis Severe fatty infiltration was observed in only 1 of 13 cases of chronic ulcerative colitis in which needle biopsy of the liver was secured at laparotomy. Kimmelstiel, Large and Verner examined the livers in 93 cases of chronic ulcerative colitis at necropsy. They found the incidence of hepatic lesions in this condition as compared with a controlled series of 1,000 necropsies to be 10 per cent and there was clinical evidence of hepatic disease in approximately 10 per cent of the cases[145] Fatty infiltration was present in 11 cases, interlobular hepatitis in 9 cases, hepatic necrosis in 8 cases, inflammatory foci in 5 cases, multiple bile casts and pseudolobulation in 2 cases each, and cirrhosis in 1 case

Thirty-two selected living patients with chronic ulcerative colitis were studied to determine the presence of hepatic disease clinically, by hepatic function tests, and by needle biopsy of the liver (Tables II, III).[153] Five patients had no morphological nor clinical evidence of hepatic disease The histological findings were normal in 5 cases, fatty infiltration in 9 cases, chronic pericholangitis in 3 cases, cirrhosis in 6 cases, chronic pericholangitis with stasis of bile in 3 cases, metastatic carcinoma in 3 cases, and acute massive necrosis in 1 case (Figs 4a, 1b, 1c, 4d) Cirrhosis was observed particularly in young adults who had had chronic ulcerative colitis from one to sixteen years There was one patient with latent portal cirrhosis, one with "intestinal infantilism," and one with portal cirrhosis and hypersplenism (Fig 5a, 5b) The clinical picture in 3 patients was cholangiolitic hepatitis Postnecrotic cirrhosis was the clinical diagnosis in 3 patients with chronic ulcerative colitis Because a small specimen of hepatic tissue was obtained by needle biopsy this diagnosis could not be verified histologically. Two patients with cirrhosis had antecedent jaundice and a cirrhotic sequela of infectious hepatitis was suspected Abnormalities of hepatic function tests were common, particularly bromsulfalein dye retention and hypoalbumenemia. Abnormal hepatic flocculation tests, hyperglobulinemia, and elevated serum bilirubin were observed in patients with inflammatory lesions of the liver and cirrhosis No correlation could be made between the hepatic lesion noted and the duration and ac-

TABLE II

Summary of clinical findings in 32 cases of chronic ulcerative colitis in which needle biopsy of the liver was performed

CASE	HEPATIC HISTOPATHOLOGIC CLASSIFICATION	SEX	AGE	DURATION OF COLITIS	ASSOCIATED CLINICAL DIAGNOSIS	LOSS OF WEIGHT	ORAL TEMPERATURE	ENLARGED LIVER	ENLARGED SPLEEN	EDEMA	ASCITES	JAUNDICE	ROENTGENOGRAPHIC INVOLVEMENT OF COLON	RECENT USE OF AUREOMYCIN OR TERRAMYCIN
			years	years		lb	°F							
1	Normal	F	31	8	Severe rectal hemorrhage	20	99	0	0	+	0	0	Entire	Yes
2	Normal	F	26	2	None	20	101	0	0	0	0	0	Entire	No
3	Normal	M	35	2	None	7	98	0	0	0	0	0	Transverse colon distally	No
4	Normal	F	24	2½	Pyoderma gangraenosum	37	98.6	0	0	0	0	0	Entire	Yes
5	Normal	F	34	17	Rectovaginal fistula	20	99.6	0	0	0	0	0	Sigmoid distally	No
6	Infiltration with fat, grade 1	F	43	4½	None	0	98.6	0	0	0	0	0	Entire	No
7	Infiltration with fat, grade 1	M	61	1½	None	12	103	0	0	0	0	0	Entire	No
8	Infiltration with fat, grade 1	M	58	2	None	10	98.6	0	0	0	0	0	Transverse colon distally	No
9	Infiltration with fat, grade 2	M	42	2	Ileofemoral phlebitis	0	99	0	0	0	0	0	Entire pseudopolyps	No
10	Infiltration with fat, grade 2	M	37	3/12	Intestinal perforation	25	101	0	0	0	0	0	Entire	Yes
11	Infiltration with fat, grade 2	F	50	1½	Severe rectal hemorrhage	10	101	0	0	0	0	0	Entire	Yes
	Infiltration with fat, grade 2	M	45	2/12	None	10	102	0	0	0	0	0	Entire	No
	Infiltration with fat, grade 3	F	22	3	Erythema nodosum	20	99	0	0	0	0	0	Entire	Yes
14	Infiltration with fat, grade 4	M	21	3	Intestinal infantilism	50	100	0	0	+	0	0	Entire	Yes

15	Pericholangitis	M	34	5	Rectal stricture	5	.086	0	0	0	0	0	Rectum	Yes
16	Pericholangitis	M	22	1½	Erythema nodosum	20	.080	0	0	0	0	0	Entire pseudopolyps	No
17	Pericholangitis	M	20	2 12	None	10	.102	0	0	0	0	0	Entire	Yes
18	Chronic pericholangitis bile stasis	M	16	6	Hepatitis	10	.09	+	+	0	0	+	Entire	Yes
19	Chronic pericholangitis bile stasis	F	42	20	Biliary cirrhosis	55	.086	0	+	0	0	+	Entire	No
20	Chronic pericholangitis bile stasis	M	50	16	Biliary cirrhosis	0	.086	+	0	0	0	+	Entire	No
21	Diffuse hepatitis	F	27	5	Biliary cirrhosis	0	.08	+	+	+	+	+	Entire	No
22	Diffuse hepatitis	M	25	10	Biliary cirrhosis	5	.09	+	+	+	0	+	Entire	No
23	Hepatic necrosis	F	50	7	Psychosis	0	.102		0	+	+	0	Entire	Yes
24	Cirrhosis	M	21	0	Cirrhosis intestinal infantilism	25	.09	+	+	0	0	0	Entire	No
25	Cirrhosis	F	29	10	Banti's syndrome	0	.08	0	+	+	0	0	Entire	No
26	Cirrhosis	M	40	10	Rectal stricture	0	.09	0	0	0	0	0	Entire	No
27	Cirrhosis	M	21	1	None	0	.080	+	0	0	0	0	Hepatic flexure distally	No
28	Cirrhosis	M	19	2½	Biliary cirrhosis	15	.100	+	+	0	0	+	Entire	No
29	Cirrhosis	M	26	6	Biliary cirrhosis	5	.086	+	+	0	0	+	Entire	No
30	Metastatic adenocarcinoma	M	50	10	Carcinoma left colon	70	.09	+	0	0	0	+	Left colon	No
31	Metastatic adenocarcinoma	F	42	11	Rectal carcinoma	20	.100	+	0	+	+	0	Entire	Yes
32	Metastatic adenocarcinoma	M	21	15	Carcinoma transverse colon	10	.09	+	0	0	0	+	Entire	Yes

TABLE II

Summary of clinical findings in 32 cases of chronic ulcerative colitis in which needle biopsy of the liver was performed

CASE	HEPATIC HISTOPATHOLOGIC CLASSIFICATION	SEX	AGE	DURATION OF COLITIS	ASSOCIATED CLINICAL DIAGNOSIS	LOSS OF WEIGHT	ORAL TEMPERATURE	ENLARGED LIVER	ENLARGED SPLEEN	EDEMA	ASCITES	JAUNDICE	ROENTGENOGRAPHIC INVOLVEMENT OF COLON	RECENT USE OF AUREOMYCIN OR TERRAMYCIN
			years	years		lb	°F							
1	Normal	F	31	8	Severe rectal hemorrhage	20	99	0	0	+	0	0	Entire	Yes
2	Normal	F	26	2	None	20	101	0	0	0	0	0	Entire	No
3	Normal	M	33	2	None	7	98	0	0	0	0	0	Transverse colon distally	No
4	Normal	F	24	2½	Pyoderma gangraenosum	37	98.6	0	0	0	0	0	Entire	Yes
5	Normal	F	34	17	Rectovaginal fistula	20	98.6	0	0	0	0	0	Sigmoid distally	No
6	Infiltration with fat, grade 1	F	43	4½	None	0	98.6	0	0	0	0	0	Entire	No
7	Infiltration with fat, grade 1	M	61	1½	None	12	103	0	0	0	0	0	Entire	No
8	Infiltration with fat, grade 1	M	58	2	None	10	98.6	0	0	0	0	0	Transverse colon distally	No
9	Infiltration with fat, grade 2	M	42	2	Ileofemoral phlebitis	0	99	0	0	0	0	0	Entire pseudopolyps	No
10	Infiltration with fat, grade 2	M	37	3/12	Intestinal perforation	25	104	0	0	0	0	0	Entire	Yes
11	Infiltration with fat, grade 2	F	30	1½	Severe rectal hemorrhage	10	101	0	0	0	0	0	Entire	Yes
12	Infiltration with fat, grade 2	M	45	2/12	None	30	102	0	0	0	0	0	Entire	No
13	Infiltration with fat, grade 3	F	22	3	Erythema nodosum	20	99	0	0	0	0	0	Entire	Yes
14	Infiltration with fat, grade 4	M	21	3	Intestinal infantilism	50	100	0	0	+	0	0	Entire	Yes

15	Pericholangitis	M	34	1	Rectal stricture	5	98.6	0	0	0	0	0	Rectum	Yes
16	Pericholangitis	M	22	1½	Erythema nodosum	20	98.6	0	0	0	0	0	Entire pseudopolyps	No
17	Pericholangitis	M	20	2½	None	10	102	0	0	0	0	0	Entire	Yes
18	Chronic pericholangitis, bile stasis	M	16	6	Hepatitis	10	99	+	+	0	0	+	Entire	Yes
19	Chronic pericholangitis bile stasis	F	42	20	Biliary cirrhosis	35	98.6	0	+	0	0	+	Entire	No
20	Chronic pericholangitis bile stasis	M	50	16	Biliary cirrhosis	0	98.6	+	0	0	0	+	Entire	No
21	Diffuse hepatitis	F	27	3	Biliary cirrhosis	0	98	+	+	+	+	+	Entire	No
22	Diffuse hepatitis	M	23	10	Biliary cirrhosis	5	99	+	+	+	0	+	Entire	No
23	Hepatic necrosis	F	30	7	Psychosis	0	102	+	0	+	+	0	Entire	Yes
24	Cirrhosis	M	21	9	Cirrhosis, intestinal infantilism	25	99	+	+	0	0	0	Entire	No
25	Cirrhosis	F	29	16	Banti's syndrome	0	98	0	+	+	0	0	Entire	No
26	Cirrhosis	M	40	16	Rectal stricture	0	99	0	0	0	0	0	Entire	No
27	Cirrhosis	M	21	1	None	0	98.6	+	0	0	0	0	Hepatic flexure distally	No
28	Cirrhosis	M	19	2½	Biliary cirrhosis	15	100	+	+	0	0	+	Entire	No
29	Cirrhosis	M	26	6	Biliary cirrhosis	5	98.6	+	+	0	0	+	Entire	No
30	Metastatic adenocarcinoma	M	30	10	Carcinoma, left colon	30	99	+	0	0	0	+	Left colon	No
31	Metastatic adenocarcinoma	F	42	11	Rectal carcinoma	20	100	+	0	+	+	0	Entire	Yes
32	Metastatic adenocarcinoma	M	21	15	Carcinoma, transverse colon	10	99	+	0	0	0	+	Entire	Yes

TABLE III

SUMMARY OF LABORATORY STUDIES IN 32 CASES OF CHRONIC ULCERATIVE COLITIS IN WHICH NEEDLE BIOPSY OF THE LIVER WAS PERFORMED

Case	Hepatic Histopathologic Classification	Hb*	RBC	WBC	Sed Rate	Ser Bil	Alk Phos	P T	A/G	SBP	T T	Z S	C C	Platelet	Blood Smear
1	d	4 4	1 38	7 600	87	0 0 5	ND	20	2.5 2 0	40	ND	ND	ND	103,000	Macrocytosis
2	d	10 2	3 81	7 800	118	0,0 5	ND	21	ND	10	18	19	4+	ND	ND
3	l	11 6	4 51	13,500	52	0 0 5	ND	19	3 8 1 6	0	ND	6	0	ND	ND
4	l	12 1	3 92	8,600	15	0 0 4	42	18	4 0 3 0	8	ND	ND	ND	ND	ND
5	l	10 4	3 49	6 600	93	0 0 2	ND	20	4 1 2 2	0	1	10	0	ND	ND
6	tion with fat 1	13 0	4 10	8 700	70	0 0 7	ND	19	4 1 2 1	10	1.5	10	0	ND	ND
7	tion with fat, 1	12 7	3 92	10 600	88	0,0 6	ND	21	3 0 2 7	32	3	4	0	ND	ND
8	tion with fat, 1	12 0	1 70	11,600	71	0/0 4	ND	19	3 4,2 5	0	3	13	0	ND	ND
9	ion with fat, 2	6 2	ND	9,800	107	0 0 4	ND	22	3 6 2 7	10	3 5	17	0	ND	Hypochromasia
10	ion with fat, 2	15.5	4 80	23,200	25	1 1,0 2	0	19	1 9,1 7	21	2	13	0	ND	ND
11	ion with fat, ,	10 8	4 01	12,300	30	0 0 5	ND	20	4 3/2 5	6	3	17	0	ND	ND
12	on with fat	11 0	3 43	4,800	133	0 0 5	5 2	22	3 9/1 5	22	1 5	6	0	ND	ND
13	on with fat	12 7	3 82	8,500	71	0,0 5	3 4	21	ND	0	2	7	3+	ND	ND
14	on with fat	10 4	3 77	8 900	53	0 0 4	5 7	21	2 0/3 1	6	1	20	1+	ND	ND
15	ngitis	16 6	4 72	9 800	15	0,1 1	ND	20	4 7 2 3	0	2	14	0	ND	ND
16	ngitis	14 6	4 51	8 200	51	0'0 7	3 1	20	4 1/2 2	0	1	6	0	ND	ND
17	ngitis	12 7	4 11	10 900	37	0 0 3	2 4	22	3 0 2 5	6	3	17	0	ND	ND
18	ericholan-e stasis	11 9	4 26	11 300	61	1 1 1/3 3	36 3	31	3 8 4 0	ND	4	26	0	341,000	Not diagnostic

19	Chronic pericholangitis, bile stasis	9.5	3.31	7 000	53	3 8 1 7	ND	20	4 2/1 9	ND	18	42	0	ND	Macrocytosis
20	Chronic pericholangitis, bile stasis	12 6	4.23	13 000	97	2 6 0 9	37 7	20	4 0 3 7	ND	3	ND	0	ND	ND
21	Diffuse hepatitis	11 9	4 32	6 900	80	11 6/2 0	10 8	20	2 9 3 5	ND	11	40	3+	137,000	Macrocytosis
22	Diffuse hepatitis	9 7	4.33	5,200	106	15.2/1 2	12	41	2 8 4 2	ND	18	49	4+	185 000	ND
23	Hepatic necrosis	11 7	4 70	13 800	35	ND	ND	21	1 8 1 7	ND	ND	ND	ND	ND	ND
24	Cirrhosis	6 4	3 31	4 800	ND	0 0 6	ND	21	3 0 3 4	12	ND	ND	0	ND	Macrocytosis
25	Cirrhosis	9 6	4 11	4 700	47	1 2 1 0	ND	22	2 9 3 2	32	ND	23	4+	25,000	Hypochromasia
26	Cirrhosis	11 8	4 30	8 000	40	0 1 0	ND	21	ND	21	3	21	0	ND	ND
27	Cirrhosis	15 0	5 04	3 600	50	0 1 2	7 4	19	4 3 3 7	28	8.5	58		ND	Macrocytosis
28	Cirrhosis	5 0	3.58	6 100	77	1 7 1 0	ND	21	3 4 3 0	24	15	61	3+	ND	ND
29	Cirrhosis	12 2	3 99	7 600	91	4 6 0 9	ND	20	4 0 3 5	ND	ND	ND	3+	ND	ND
30	Metastatic adenocarcinoma	15 0	3 98	11 100	70	2 6 1 5	33 9	29	4 1 3 5	ND	2	6	2+	ND	ND
31	Metastatic adenocarcinoma	8 9	3 64	5,500	70	ND	ND	25	2 3 2 2	ND	ND	ND	ND	ND	ND
32	Metastatic adenocarcinoma	12 7	4 92	7 700	49	2 1 0 8	ND	21	ND	32	ND	ND	ND	ND	ND

* Abbreviations Hb = hemoglobin gm 100 cc blood RBC = erythrocytes millions cu mm WBC = leukocytes cu mm Sed rate = erythrocyte sedimentation rate mm 1 hour (Westergren) Ser bil = serum bilirubin mg 100 cc Alk phos = serum alkaline phosphatase mg 100 cc (Bodansky), P T = plasma prothrombin time (normal 17–19 sec) S A G = serum albumin globulin gm 100 cc BSP = Sulfobromophthalein retention, per cent T T = thymol turbidity units Z S = (Kunkel) zinc sulfate units, C.C. = cephalin cholesterol flocculation, platelet = platelets cu mm blood and ND = not done

(Kleckner M S Jr Stauffer M H Bargen J A and Dockerty M B Gastroenterology Sept 1952)

TABLE III

SUMMARY OF LABORATORY STUDIES IN 32 CASES OF CHRONIC ULCERATIVE COLITIS IN WHICH NEEDLE BIOPSY OF THE LIVER WAS PERFORMED

Case	Hepatic Histopathologic Classification	Hb*	RBC	WBC	Sed Rate	Ser Bil	Alk Phos	P T	A/G	SBP	T T	Z S	C C	Platelet	Blood Smear
1	Normal	4.4	1.38	7,600	87	0/0.5	ND	20	2.5/2.0	40	ND	ND	ND	105,000	Macrocytosis
2	Normal	10.2	3.81	7,800	118	0/0.5	ND	21	ND	10	18	49	4+	ND	ND
3	Normal	11.6	4.51	13,500	52	0/0.5	ND	19	3.8/1.6	0	ND	6	0	ND	ND
4	Normal	12.4	3.92	8,600	15	0/0.4	4.2	18	4.0/3.0	8	ND	ND	ND	ND	ND
5	Normal	10.4	3.49	6,600	93	0/0.2	ND	20	4.1/2.2	0	1	10	0	ND	ND
6	Infiltration with fat grade 1	13.0	4.40	8,700	70	0/0.7	ND	19	4.1/2.4	10	1.5	10	0	ND	ND
7	Infiltration with fat, grade 1	12.7	3.92	10,600	88	0/0.6	ND	21	3.0/2.3	32	3	4	0	ND	ND
8	Infiltration with fat, grade 1	12.0	4.70	11,000	71	0/0.4	ND	19	3.4/2.5	0	3	13	0	ND	ND
9	Infiltration with fat, grade 2	6.2	ND	9,800	107	0/0.4	ND	22	3.6/2.7	10	3.5	17	0	ND	Hypochromasia
10	Infiltration with fat, grade 2	15.5	4.80	23,200	25	1.1/0.2	0	19	1.9/1.7	24	2	13	0	ND	ND
11	Infiltration with fat, grade 2	10.8	4.01	12,300	30	0/0.5	ND	20	4.3/2.5	6	3	17	0	ND	ND
12	Infiltration with fat, grade 2	11.0	3.43	4,800	133	0/0.5	5.2	22	3.9/1.5	22	1.5	6	0	ND	ND
13	Infiltration with fat, grade 3	12.7	3.82	8,500	71	0/0.5	3.4	21	ND	0	2	7	3+	ND	ND
14	Infiltration with fat, grade 4	10.4	3.77	8,900	53	0/0.4	5.7	21	2.0/3.1	6	1	20	1+	ND	ND
15	Pericholangitis	16.6	4.72	9,800	15	0/1.1	ND	20	4.7/2.3	0	2	14	0	ND	ND
16	Pericholangitis	14.6	1.51	8,200	31	0/0.7	3.1	20	4.4/2.2	0	1	6	0	ND	ND
17	Pericholangitis	12.7	4.11	10,900	37	0/0.5	2.4	22	3.0/2.5	6	3	17	0	ND	ND
18	Chronic pericholangitis, bile stasis	11.9	4.26	11,500	61	1.1/3.3	36.3	31	3.8/4.0	ND	4	26	0	311,000	Not diagnostic



FIG. 56 Histological specimen of liver, same case at two years. Moderate to marked fatty infiltration, probably insignificant round cell parenchymal status and perilobular and portal fibrosis (H & E ×120)

hepatitis, hemorrhagic shock, absorption of large numbers of bacteria from the intestinal flora, pancreatitis, and sepsis are conditions that may contribute to the production of hepatic lesions in chronic ulcerative colitis.

BRUCELLOSIS

The involvement of the liver in patients with brucellosis has been recognized particularly since the advent of needle biopsy and this technique is currently employed as a diagnostic tool. An enlarged liver occurs in about 10 per cent of patients with brucellosis. Jaundice, hepatosplenomegaly, and ascites have been reported to be clinical features of brucellosis.[117, 119, illegible, 292] The various types of hepatic lesions associated with this granulomatous disease include necrosis, hepatitis, suppuration, calcification, granulomas, and cirrhosis.[47, 52, 112, 117, 119, 124, 129, illegible, 239, 244, 254, 272]

The progression of brucella hepatitis to cirrhosis is documented in a few instances. Rothenberg reported a case of brucellosis in a



FIG 5a Hepatomegaly in a thirteen year old boy with segmental or regional chronic ulcerative colitis of two and a half years' duration; arrest of maturation and impaired growth, so-called "intestinal infantilism", battery of hepatic function tests were essentially normal Proctosigmoidoscopy and three initial air-contract roentgenograms of the colon and small intestine were considered normal Prompt and continued benefit of medical therapy

tivity of the colitis, administration of blood or plasma, malnutrition, loss of weight or the extent of involvement of the colon by ulcerative colitis.

The etiology of various types of hepatitis and cirrhosis associated with chronic ulcerative colitis is obscure. Fatty infiltration, on the other hand, may be the result of malnutrition, intestinal malabsorption, intestinal resection, inanition, fever, therapy with broadspectrum antibiotics and corticosteroids, and intestinal loss of blood and protein through rectal discharges. Anemia, viral

in cases of severe brucella hepatitis when the patient has concurrent hepatic disease, imbibes alcohol or is malnourished.

Two patients with brucellosis of interest have been observed with hepatic involvement. One, a sixty two year old woman, complained of fever, chills, anorexia, jaundice, tenderness over the liver, prostration, and marked loss in weight. She had an enlarged liver, and an enlarged spleen and was jaundiced. Needle biopsy of the liver revealed a diffuse hepatitis (Fig. 6a). She was treated intensively with tetracycline. The laboratory tests were as follows: direct serum bilirubin, 11.4, total serum bilirubin, 17.4 mg./100 cc., serum albumin, 3.7 gm., serum globulin, 2.9 gm./100 cc., serum alkaline phosphatase, 12.1 Bodansky units, cephalin-cholesterol flocculation, 2+, prothrombin time was 50 per cent of normal, and erythrocyte sedimentation rate was 45 mm./hour (Westergren). Brucella abortus was cultured from the blood. One year later, the patient returned for a re-evaluation. Needle biopsy of the liver and the hepatic function tests were normal. This patient had had an active brucella hepatitis, and it would appear if intensive, prolonged antibiotic therapy had not been administered, such as was impossible in the pre-antibiotic era, this might conceivably have progressed to brucella cirrhosis.

Another patient was observed complaining of weakness, and pain over the region of the liver. He had been told that he had brucellosis several years earlier. Needle biopsy of the liver revealed a portal cirrhosis but without miliary granulomata. Several weeks later, the patient returned with high fever, chills and marked ascites. Brucellosis was suspected but this organism could not be cultured repeatedly from the blood. The brucella agglutination titer was positive, 1:3,200. Another needle biopsy of the liver performed following adequate diuresis, disclosed no change in the histologic appearence of the liver, but brucella abortus were cultured from part of the hepatic specimen.[7,53] The patient died several months later in hepatic coma. Had miliary granulomata been observed in the hepatic biopsy, one might have concluded this case to be a brucella cirrhosis. It would appear that a diagnosis of brucella cirrhosis can be established only when there is histological evidence of cirrhosis and miliary granulomata of the liver, and a positive blood

fifty-seven year old man who complained of cough, fever, perspiration, joint pains, and shortness of breath[235] Ascites, pleural effusion, and atrophic cirrhosis were demonstrated at necropsy. Schittenhelm reported the occurrence of cirrhosis as a sequela to brucellosis in several cases[239] Cohen studied 53 cases of brucellosis at the Wisconsin General Hospital. He reported a case of a twenty-two year old man whose findings at necropsy disclosed a coarsely nodular cirrhosis.[53] Spink and his co-workers performed needle biopsies of the liver on 10 patients with brucellosis and cirrhosis and were unable to distinguish between the hepatic granulomata seen in this disease and in sarcoidosis.[254] He was of the opinion that a direct relationship between brucellosis and cirrhosis had not been established, but there was accumulating evidence that brucellosis may play an important role in the morphogenesis of cirrhosis McCoy reported a fatal case of brucellosis complicated by cirrhosis of the liver[182]

McCullough and Eisele report an unusually well-documented case of Brucella hepatitis progressing to cirrhosis of the liver[183] Their patient was a fifty-two year old man with brucellosis in whom a needle biopsy showed hepatitis and hepatic granulomatosis The patient had jaundice, enlarged liver, palmar erythema, leukopenia, positive hepatic flocculation studies, reversal of the albumin and globulin ratio and a moderate normocytic anemia Two years later the liver was palpated and was found to be enlarged, hard and nodular In addition, there was retention of the bromsulfalein dye and abnormal thymol turbidity and cephalin flocculation tests Biopsy of the liver at that time disclosed cirrhosis of the liver The case is unique because it is an established case of serial needle biopsies of the liver and hepatic function tests which disclose the transition of brucella hepatitis to cirrhosis. These authors comment on the extensive European references that have accumulated on the occurrence of hepatitis and brucellosis and its progression to cirrhosis[129,165a,244]

Hoffbauer observed two cases of fatal cirrhosis and considered the infectious pathogenesis[119] He could not find any other specific cause for the cirrhosis other than the associated brucellosis It may be that occasionally brucellosis may augment cirrhosis particularly

in cases of severe brucella hepatitis when the patient has concurrent hepatic disease, imbibes alcohol or is malnourished.

Two patients with brucellosis of interest have been observed with hepatic involvement. One, a sixty two year old woman, complained of fever, chills, anorexia, jaundice, tenderness over the liver, prostration, and marked loss in weight. She had an enlarged liver, and an enlarged spleen and was jaundiced. Needle biopsy of the liver revealed a diffuse hepatitis (Fig. 6a). She was treated intensively with tetracycline. The laboratory tests were as follows: direct serum bilirubin, 11.1, total serum bilirubin, 17.1 mg./100 cc., serum albumin, 3.7 gm.; serum globulin, 2.9 gm./100 cc., serum alkaline phosphatase, 12.1 Bodansky units; cephalin-cholesterol flocculation, 2+, prothrombin time was 50 per cent of normal, and erythrocyte sedimentation rate was 13 mm./hour (Westergren). Brucella abortus was cultured from the blood. One year later, the patient returned for a re-evaluation. Needle biopsy of the liver and the hepatic function tests were normal. This patient had had an active brucella hepatitis, and it would appear if intensive, prolonged antibiotic therapy had not been administered, such as was impossible in the pre-antibiotic era, this might conceivably have progressed to brucella cirrhosis.

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Fig 6a Histological specimen of Brucella hepatitis Needle biopsy of liver. The lesion was indistinguishable from acute viral hepatitis (H & E, X120).
Fig 6b Histological specimen of hepatic granulomas, so called granulomatous hepatitis Diagnostic confirmation by blood culture and agglutination test Needle biopsy of the liver Hepatic rather than blood culture confirmed the diagnosis of Brucella abortus Patient neither had nor had had clinical evidence of liver disease (H & E, X80).

or hepatic biopsy culture for brucella, especially when the pathogenesis of cirrhosis cannot be explained by other more common means (Fig 6b).

INFECTIOUS MONONUCLEOSIS

The liver has commonly been affected in patients with infectious mononucleosis. Hepatic dysfunction, particularly as represented by abnormal retention of bromsulfalein dye and hepatic flocculation tests has been found in approximately 75 per cent of cases.[8,24,27,46,50,61,97,112,121,136,212,257,260,279,280] Anicteric and icteric hepatitis as the result of infectious mononucleosis is a frequent complication.[11,22,24,35,65,67,70,74,78,99,140,195,202,278] Jaundice has been reported in 1 to 13 per cent and hepatosplenomegaly in approximately 30 per cent patients with infectious mononucleosis.[7,23,49,50,54,92,120,125,126,140,175,184,192,195,250,260]

Two patients with cirrhosis following infectious mononucleosis have been reported.[163,207] Leibowitz and Brady describe such an instance in a twenty four year old male. Three years after infectious mononucleosis occurred, cirrhosis was verified by needle biopsy of the liver.[165] However, alcoholism and malnutrition present in this case discredit accurate pathogenesis. In general, the rare occurrence of cirrhosis and the relative frequency of hepatic dysfunction hepatitis in infectious mononucleosis seem to indicate that the repair of the liver, is normal following this hepatic infection of low virulence, or it may cause low-grade hepatocellular injury in young adults in which the process of hepatic regeneration is normal.

KALA-AZAR

Cirrhosis has been attributed or associated with kala azar or visceral leishmaniasis in several reports.[26-28,51,123,130,153,225] The protozoal parasite of this infestation, Leishman-Donovan bodies, has been considered the cirrhotogenic agent in these reports. Some investigators have stated that dietary deficiency should be considered a contributing factor of cirrhosis in patients with parasitic disease since it is doubtful that parasites can cause cirrhosis.[49,201,216,261,262] Rogers has described an unusual intralobular cirrhosis due to the Leishman-Donovan bodies in certain patients after several years of illness from kala azar.[225] These protozoa multiply in the reticulo-

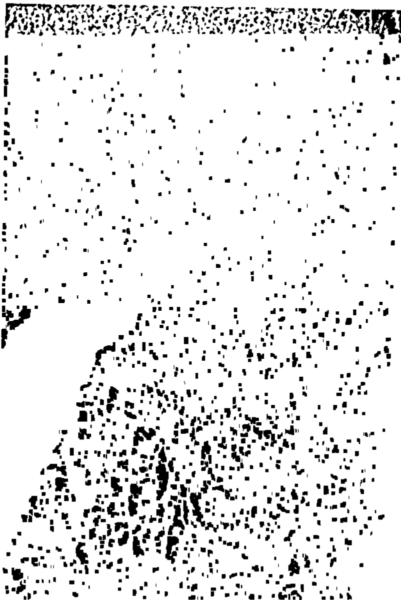


FIG 6a Histological specimen of Brucella hepatitis Needle biopsy of liver The lesion was indistinguishable from acute viral hepatitis (H & E, X120)
FIG 6b Histological specimen of hepatic granulomas, so called granulomatous hepatitis Diagnostic confirmation by blood culture and agglutination test Needle biopsy of the liver Hepatic rather than blood culture confirmed the diagnosis of Brucella abortus Patient neither had nor had had clinical evidence of liver disease (H & E, X80).

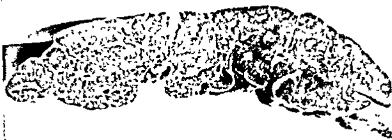


FIG. 7b Gross sagittal specimen of the same liver. Marked portal fibrosis surrounding portal veins absence, however, of regenerative nodules (Courtesy, Bagliolo L.)



FIG 7c Venyl cast of portal tree of liver from a case of schistosomiasis mansoni Preservation of general architecture of portal tree which has become thick and coarse by fibrosis and vascular ramifications (Courtesy Bagliolo L.)

tralobular fibrosis, preservation of lobular architecture, intralobular mechanical obstruction of sinusoidal and central venous flow of blood, and hyperplasia of the Kupffer cells The clinical findings of this disease are cutaneous sores, low-grade fever, hepatosple-

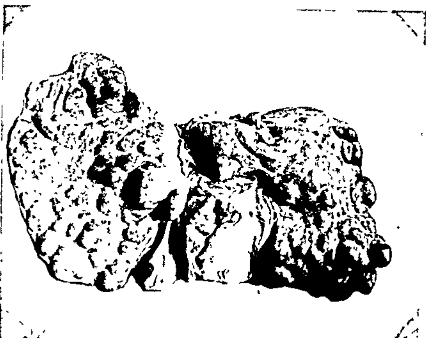


FIG 7a Gross specimen of liver Schistosomiasis mansoni, "Pipe-stem" cirrhosis Pseudo nodules This appearance grossly suggests postnecrotic cirrhosis (Courtesy, Bogliolo, L)

endothelial cells of the liver, spleen and bone marrow Hyperplastic connective tissue with little alteration in the hepatic lobular arrangement and absent regenerative nodules were the outstanding morphological features of the liver in this condition The patients were natives of Calcutta and the lower Bengal area of India Four of forty-eight necropsy cases had cirrhosis following several years illness from kala-azar. Kala-azar associated with cirrhosis has been described in Chinese patients in which the cirrhosis resembles Roger's description [31]

Bogliolo has reported cirrhosis occurring in patients with kala-azar in Brazil and has compared the morphological findings of the liver with hepatic schistosomiasis [26-28] Hepatic fibrosis, or so-called pipe-stem cirrhosis, is observed in the latter condition, and portal hypertension is considered the result of intrahepatic fibrotic occlusion of the portal veins (Fig. 7, 8).[26-28 66 262] He described an in-

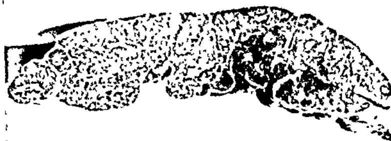


FIG. 7b Gross sagittal specimen of the same liver. Marked portal fibrosis surrounding portal veins, absence, however, of regenerative nodules. (Courtesy, Bagholo L.)



FIG. 7c Vinyl cast of portal tree of liver from a case of schistosomiasis mansoni. Preservation of general architecture of portal tree, which has become thick and coarse by fibrosis and vascular ramifications. (Courtesy, Bagholo L.)

tralobular fibrosis, preservation of lobular architecture, intralobular mechanical obstruction of sinusoidal and central venous flow of blood, and hyperplasia of the Kupffer cells. The clinical findings of this disease are cutaneous sores, low-grade fever, hepatosple-

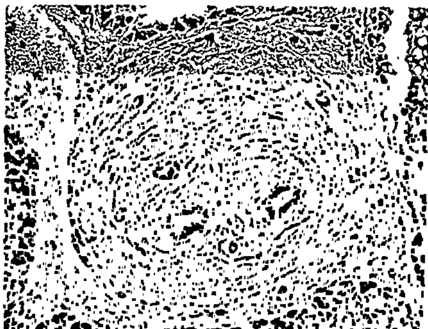


FIG 7d Histological specimen of a portal area in a liver with schistomiasis mansoni Marked portal fibrosis and almost complete obliteration of portal vein (H & E, X400) (Courtesy, Bogliolo, L.)

nomegaly, emaciation, jaundice, ascites, edema, anemia, and bronchitis.

FLORID CIRRHOSIS

Popper and his associates in 1955 described an unusual type of hepatic *disease—florid cirrhosis—that defied classification* and was frequently encountered at necropsy[221] Actually this usually fatal condition had been referred to as subacute portal cirrhosis, progressive alcoholic cirrhosis, subacute alcoholic noncirrhogenous hepatitis, and chronic toxic hepatitis[4, 108, 108, 214, 216, 219, 219] *Alcoholism* was observed in 86 per cent and malnutrition in 43 per cent They noted gastro-intestinal pain, anorexia, nausea and vomiting in 80 per cent of the patients, weakness and weight loss in 45 per cent, pulmonary complaints, cough and fever in 37 per cent, and bleeding from the gums, epistaxis, disorientation and coma in 20 per cent, and gastrointestinal hemorrhage in 17 per cent of the cases

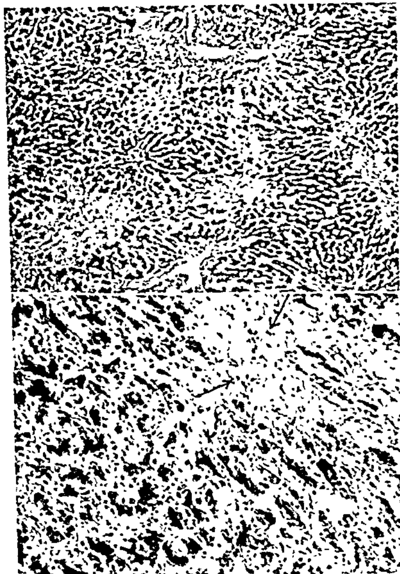


FIG. 8a. Histological specimen of liver. Kala-azar in Brazil. Note preservation of parenchymal architecture with intralobular fibrosis and atrophy. (H & E, approximately X250) (Courtesy, Bigliolo, L.)

FIG. 8b. Increased magnification of histological features of same case. Intralobular and perisinusoidal fibrosis. Thickness of walls of sinusoids, atrophy of hepatic parenchyma (marked by arrows). (H & E, approximately X1,200) (Courtesy, Bigliolo, L.)

Patients with this condition have marked hepatic insufficiency. Jaundice was found in 91 per cent of cases, cholemia in 73 per cent, ascites in 43 per cent and peripheral edema in 14 per cent. Biochemical studies of this condition disclosed hyperbilirubinemia, abnormal hepatic flocculation tests, elevation of the serum alkaline phosphatase, hypoalbuminemia, hyperglobulinemia, and leukocytosis. In all of the patients, the icterus index exceeded 100 units and the cephalin-cholesterol flocculation tests was abnormal. This hepatic condition was frequently associated with bronchopneumonia, tuberculosis, hemorrhagic tracheobronchitis, and lobar pneumonia.

The term, "florid cirrhosis," was proposed for the early stage of this hepatic disease, because survivors could be expected eventual-

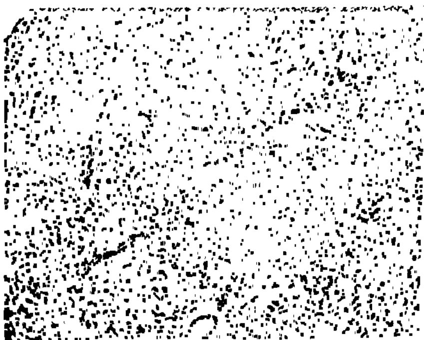


FIG 9 Histological findings from an alcoholic, malnourished case of "florid cirrhosis" or "chronic toxic hepatitis" Marked fatty infiltration and hepatocellular damage Stasis of bile and production of stroma Incipient septa formation, hepatocellular focal regeneration and collapse of reticulum network, which would usually produce cirrhosis, providing the patient would survive (H & E, X100)

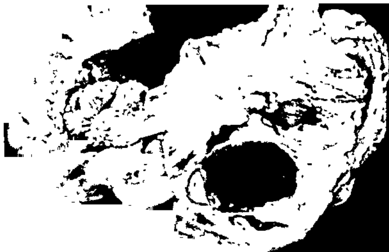


FIG 10a Sagittal section of specimen of the gross pancreas Chronic relapsing pancreatitis, fatty infiltration, marked atrophy and fibrosis of the pancreas, large necrotic pseudocyst

ly to succumb from portal cirrhosis This condition has been regarded as a link between fatty liver and cirrhosis [114 219 220] Grossly, the liver is usually enlarged, doughy and green, yellow- or brown-colored The surface is usually smooth, but foci of fine granularity were noted in 29 per cent of Popper's patients Small, sharply defined regenerative nodules, 2 to 3 mm in diameter, were noted in a few areas of almost every liver Histologically, florid cirrhosis may be interpreted with some difficulty from viral hepatitis. Focal fatty infiltration, Mallory alcoholic-hyaline bodies, severe hepatocellular degeneration and necrosis, parenchymal infiltration with polymorphonuclear leukocytes, and fibrosis extending irregularly throughout the parenchyma are the significant histological findings (Fig 9).

ACUTE AND CHRONIC RELAPSING PANCREATITIS

The relationship between pancreatitis and various hepatic lesions has been cited in several reports Outstanding examples al-

luded to in earlier chapters are the concurrence of pancreatic lesions and cirrhosis in alcoholic malnourished patients and in those with hemochromatosis, kwashiorkor, diabetes mellitus, chronic ulcerative colitis, and fibrocystic disease of the pancreas. Fatty infiltration of the liver and portal cirrhosis have been reported in patients with acute pancreatitis, chronic relapsing pancreatitis, and carcinoma of the pancreas (Fig. 10b).[50,56,57,69,77,78,85,87,88,90 91,208,236,247,]



FIG. 10b. Gross specimen of the liver, spleen, and pancreas, chronic relapsing pancreatitis occurring in a fifteen year old male and confirmed morphologically Well-developed, latent portal cirrhosis, congestive splenomegaly and a fibrotic, fatty, atrophic pancreas containing small intraductal calculi Death was due to septicemia during the pre-antibiotic era Note large lobules appearing on the surface of the cirrhotic liver resembling postnecrotic repair. Actually, granular regenerative nodules characterized the type of cirrhosis During lifetime abdominal pain, malnutrition, and recurrent infections were persistent conditions, death resulting from septicemia



Fig. 10c Histological specimen of liver of Figure 10b. Typical findings of portal cirrhosis and marked fatty infiltration (H & E ×200)

[265 269 255] The intimate association between fatty liver and pancreatic fibrosis and lithiasis impressed Cole and Howe so much that they referred to this entity as the "pancreaticohepatic syndrome" in adults.[56] Snell and Comfort described two patients with chronic relapsing pancreatitis and cirrhosis and also suggested a pathogenetic relationship.[247] Sanes and his associates reported 7 cases of chronic relapsing pancreatitis in which the liver disclosed fatty infiltration and/or portal cirrhosis.[236] Fisher and McCoy studied 14 consecutive cases of acute hemorrhagic pancreatitis at necropsy.[91] Hepatic lesions, exclusive of fatty infiltration were observed in 11 cases, hepatic necrosis in 5 cases, bile stasis in 7 cases, pericholangitis in 1 case, and nuclear pleomorphism and mitoses in 3 cases. The frequency of hepatic necrosis, viral hepatitis, and fatty infiltration of the liver has been confirmed by others in cases of acute hemorrhagic pancreatitis.[3 75 157 239 297]

Pancreatic lesions have been described in association with cirrhosis. The frequency of interstitial fibrosis of the pancreas has been described in cirrhosis.[143 255 256] Stinson, Baggenstoss, and Morlock studied, under a controlled method, the pancreas in 75 cases with cirrhosis observed at necropsy.[256] Alcoholism had been recorded in

29 of these. Interstitial leukocytic reaction was observed in 51 cases, fibrosis in 59 cases, parenchymal necrosis in 14, and calcification in 5. Some degree of acinar dilatation was present in 36 and ductal dilatation was observed in 25 of the 75 cases. These observers doubted whether these pancreatic lesions would affect in any way functional efficiency of the pancreas and tended to confirm the studies of Gross and his associates who found no evidence of pancreatic functional impairment in patients with parenchymal disease of the liver.[104]

While the effect of hepatic and pancreatic lesions upon one another remains conjectural, there are severe factors which may produce simultaneous lesions. These are obstructive lesions in the extrahepatic biliary tract, pancreatic reflux, toxins, alcohol, vomiting, shock, malnutrition, diabetes mellitus, pancreatic exocrine deficiency, and steatorrhea.[10,13,91,178,236,247,258] The administration of ethionine, the metabolic antagonist of methionine, pancreatectomy, and deficiency of lipocaic or choline have caused either fatty livers or cirrhosis and pancreatic lesions in experimental animals.[5,75,83]

THE DE TONI-FANCONI SYNDROME

The de Toni-Fanconi or Fanconi syndrome is an idiopathic familial condition characterized by hepatosplenomegaly, dwarfism, pseudofractures (Milkman syndrome), renal glycosuria, aminoaciduria, hypophosphatemia, hyperphosphaturia, rickets, acidosis, steatorrhea, generalized cystinosis, and cystinuria, albuminuria, increased alkaline phosphatase and urine ammonia. It is invariably fatal before puberty. It generally occurs in children between the ages of two and five years but has been reported in adults.[275] The disease is considered by some to be due to a congenital enzymatic defect in the proximal convoluted renal tubules with impaired reabsorption of amino acids, glucose, phosphate, bicarborate, potassium, and sodium.[60,72,83,84,258] Dent has also described abnormalities in the metabolism of methionine and alpha, amino-butyric acid.[71] Postnecrotic cirrhosis, while not a primary feature of the Fanconi syndrome, has been reported in this condition in several instances.[12,71,116,297] Stowers and Dent reported fatty liver and focal hepatic necrosis in the Fanconi syndrome.[259] Himsworth reported

two cases of hepatoma with cirrhosis in this condition (Fig. 11).[119] Congenital cirrhosis has been described in a child who died at two one-half years of age with the Fanconi syndrome.[17] Himsworth has stated that hepatic lesions and splenomegaly develop, however, only in cases with amino-aciduria.[119] It is conceivable that amino-aciduria and/or increased storage of cystine in the liver might be the causative factors of cirrhosis in this condition.



FIG. 11. Specimen of liver showing postnecrotic cirrhosis with the de Toni-Fanconi syndrome in a man thirty four years of age. Carcinomatous change was present in one of the nodules on the posterior surface of the liver. (Courtesy, Himsworth, H. P.—The Liver and its Diseases—Cambridge, Harvard, 1950.)

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Chapter 14

PORTAL HYPERTENSION

THE TERM "portal hypertension" was first employed in this country by Sir Archibald H McIndoe in 1928 during his classical experiments on cirrhosis to connote elevation of pressure in the portal vein. He considered that if a simple Eck fistula could be performed in cases of cirrhosis, "portal hypertension would be relieved, stasis immediately abolished, and the development of varices arrested" [201] Earlier descriptions of this condition by European and American investigators in the Eighteenth and Nineteenth Centuries had failed to make clear the association of cirrhosis as a pathogenetic factor An exception was Frerichs who in 1879 associated esophageal varices and splenomegaly with cirrhosis in his outstanding book on diseases of the liver.[121] In 1883 Banti reported on the syndrome of splenic anemia and considered cirrhosis as its terminal stage [15-18] According to Child it was after 1900 when Gilbert and Weil, Villaret, and Pichancourt recorded directly elevated portal vein pressures and stated that esophageal varices were considered manifestations of portal hypertension [26,59,109,141,142,156,204,295-297] Larrabee in 1934 and Rousselot in 1936 independently designated the liver as the site of obstruction in patients with cirrhosis and manifestations of portal hypertension.[171,264] The results of these early investigations soon paved way for the routine operative determinations of measuring pressure in the portal and splenic veins, and the surgical establishment of a venous shunt between the portal and systemic veins in an effort to decompress the elevated pressure in the portal vein in patients with cirrhosis While such a surgical procedure is not intended to improve the hepatocellular function of the diseased liver other than to protect it from repeated loss of blood due to hemorrhages from esophageal varices, this constitutes the most rational, physiological, and effective treatment of portal hypertension known today in patients with cirrhosis.

PATHOLOGICAL PHYSIOLOGY OF PORTAL HYPERTENSION

Aware of the major anatomical variations of the portal vein and its tributaries, Gilfillan, and Douglass, Baggenstoss, and Hollinshead, respectively studied the portal venous system at necropsy and portrayed a variety of patterns most frequently encountered (Fig 1) [87,88,126] In the latter series of 92 subjects, the tributaries of the portal vein were found to be the splenic, superior mesenteric, superior pancreaticoduodenal, and pyloric veins However, the inferior mesenteric vein was found anastomosed to the portal vein in 29 3 per cent of the cases, the coronary vein in 21 1 per cent and the right gastroepiploic vein in 2 2 per cent. The importance of their findings is obvious when accurate identification of the portal venous system is necessary at the time of portacaval shunt procedures in patients with cirrhosis After the portal vein enters the liver it divides into a right and left trunk supplying venous blood to separate territories of the liver [104,202]

Approximately 75 per cent of the blood flowing through the liver comes from the portal vein. This blood, while too inadequately oxygenized for the liver, is, nevertheless, rich in nutrient absorbed from the small intestine The remaining 25 per cent of the blood is derived from the hepatic artery, which furnishes, principally, oxygen and maintains a blood pressure gradient in the hepatic sinusoids, resulting in resistance to flow of blood from the portal vein It seems reasonably certain also that arterioportal venous anastomoses called "valves of Gad" are normally present in the liver whereas the existence of shunts between the hepatic vein and portal vein are doubtful [76,104,105,193,245,270,299]

The morphological features characteristic of cirrhosis (Chapter 3), in particular nodular regeneration and arteriovenous anastomosis appear to influence hepatic circulation and portal hypertension significantly For a long time, fibrosis of the liver in cirrhosis was considered responsible for producing an increase in tissue tension by contracting and constricting the regenerative nodule [176,202] More recently, the important role of the regenerative nodule in increasing tissue tension, compressing and distorting the hepatic blood supply, augmenting arterioportal anastomosis, and producing

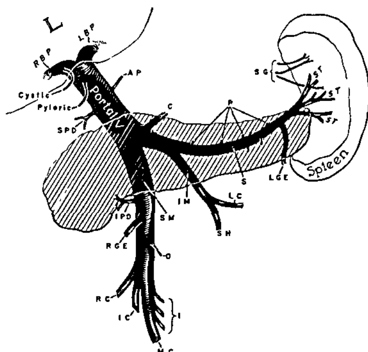


Fig. 1 The extrahepatic portal system of veins, anterior aspect The termination of each vein as it was encountered most frequently in the 92 dissections The pancreas is represented by the shaded area

A P—accessory pancreatic vein, C—coronary vein, Cystic—cystic vein, I—intestinal veins, I C—ileocolic vein, I M—inferior mesenteric vein, L C—Left colic vein, L G E—left gastroepiploic vein, M C.—middle colic vein, O—omental vein, P—pancreatic veins, Pyloric—pyloric vein; R B. P—right branch of portal vein, R C—right colic vein, R G E—right gastroepiploic vein, S—splenic vein; S G—short gastric veins, S H—superior hemorrhoidal vein; S M.—superior mesenteric vein, S P D—superior pancreatico duodenal vein, S T.—splenic trunks

(Drawing by Dorothy Booth). (Courtesy, Dougless, B E, Baggenstoss, A H, and Hollinshead, W. H—Proc Staff Meet, Mayo Clin—January 8, 1950)

portal hypertension in the cirrhotic liver has been the contention of many investigators [8,83,86,104,105,139,164,165,169,187,192,194,195,200,306] Volwiler and Gardner, respectively, have produced "silica fibrosis" experimentally, in which nodular regeneration is inconspicuous, and

which has resulted in marked portal hypertension and collateral venous circulation without esophageal varices.[1274, 294] Rousselot produced the same results, but with esophageal varices[213] Reconstructed cirrhotic livers or models have demonstrated that the intrahepatic venous obstruction is due to the regenerative nodule, the latter being supplied mainly by arterial blood (Fig. 2). Little *wonder is it that portal hypertension then is significantly reduced* by hepatic artery ligation and that hepatic ischemic necrosis and insufficiency invariably result[240]

As the result of various perfusion studies on cirrhotic livers,



FIG 2a Portion of the cast of a normal liver (X2½). Interdigitation of the portal vein with its accompanying hepatic artery and the hepatic vein, the uniformity of the ramification is apparent

FIG 2b Zonal variation in filling The light area is filled predominantly from the hepatic artery, whereas the dark area is filled from the portal vein

The portal vein and its tributaries

Fig. 1 The extrahepatic portal system of veins, anterior aspect. The termination of each vein as it was encountered most frequently in the 92 dissections. The pancreas is represented by the shaded area.

A. P.—accessory pancreatic vein, C.—coronary vein; Cystic—cystic vein, I.—intestinal veins, I. C.—ileocolic vein, I. M.—inferior mesenteric vein, L. C.—Left colic vein, L. G. E.—left gastroepiploic vein; M. C.—middle colic vein; O.—omental vein, P.—pancreatic veins, Pyloric—pyloric vein, R. B. P.—right branch of portal vein, R. C.—right colic vein, R. G. E.—right gastroepiploic vein, S.—splenic vein, S. G.—short gastric veins, S. H.—superior hemorrhoidal vein, S. M.—superior mesenteric vein, S. P. D.—superior pancreatico-duodenal vein; S. T.—splenic trunks

(Drawing by Dorothy Booth) (Courtesy, Dougless, B. E., Baggenstoss, A. H., and Hollinshead, W. H.—Proc. Staff Meet., Mayo Clin.—January 8, 1950.)

portal hypertension in the cirrhotic liver has been the contention of many investigators [8, 63, 66, 104, 105, 139, 164, 165, 169, 187, 192, 194, 195, 299, 308]. Volwiler and Gardner, respectively, have produced "silica fibrosis" experimentally, in which nodular regeneration is inconspicuous, and

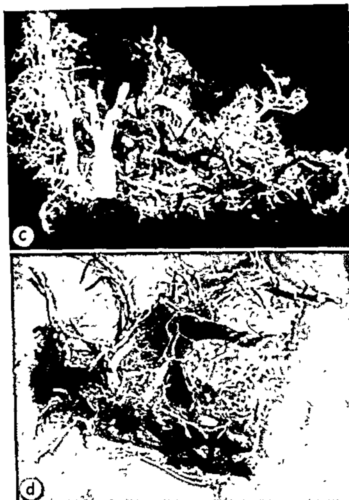


FIG 2c Portion of a cast of a postnecrotic liver (X3) Note distortion of all vascular elements, the abnormal contour of the hepatic vein (white) is especially evident

FIG 2d Baskets of vessels in the septa between regenerative nodules (Courtesy, Mann, J D, Wakim, K G, and Baggenstoss, A H—*Gastroenterology*—December 1953)

Herrick's original classic work has been confirmed.[22,83,96,111,112] It has been demonstrated that there is an increase in arterial blood flow, unimpeded portal blood flow and arteriovenous anastomoses in experimental cirrhotic livers. The pressure in the portal vein in these studies was influenced markedly by the hepatic arterial pressure. Herrick's perfusion experiments revealed that at an arterial blood pressure of 130 mm of mercury in the normal liver, blood flows into the portal vein under a pressure of 13 to 14 mm of mercury, and that in a cirrhotic liver the portal venous pressure is elevated to 30 to 40 mm of mercury.[112] This hemodynamic feature of cirrhosis was not confirmed by McIndoe, who found that as cirrhosis becomes advanced the stroma obliterates the portal venous blood supply to the liver.[201] Nevertheless, the consensus is that portal hypertension in the cirrhotic liver is the result principally of intrahepatic venous obstruction as the consequence of nodular regeneration, hepatic arteriovenous shunts, and, finally, hypervolemia related to a greater blood supply flowing through the hepatic artery. Reduction in the clearance of bromsulfalein dye in portal hypertension in experimental cirrhosis and partial hepatectomy as demonstrated by Bollman and Grindley would appear to indicate shunting of portal blood through the liver as the result of hepatic nodular regeneration.[44]

As the result of these abnormal hemodynamics and abnormal hepatic vasculature in cirrhosis, there develops naturally a collateral venous circulation, which has been labeled by Pick and McIndoe as "the hepatopedale" and "the hepatofugale."[201,242] The hepatopedale vessels shunt the blood from the portal vein and consist of the veins of Sappey or accessory portal veins. They convey the blood into the liver in extrahepatic portal vein obstruction and connect the capsule of the liver with the lumbar and diaphragmatic regions. These collateral veins are the hepatocolic, hepatorenal, deep cystic and diaphragmatic veins, and the veins in the gastrohepatic omentum and the suspensory ligament. More important collateral venous channels are the hepatofugale vessels which shunt venous blood from the portal vein to the abdominal viscera or the parietal peritoneum. These vessels are the most significant collateral veins in cirrhosis of which the most important are esophageal and gastric varices, hemorrhoids, veins of Retzius, and "caput

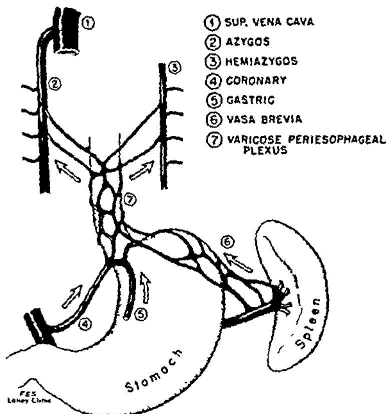


FIG 3b Portal hypertension Collateral portal shunts are established anastomosing the Vasa brevia and left gastric veins of the valveless portal veins with the azygos and hemiazygos veins (Courtesy, Sedgwick, C. E., and Parrish, C M.—Surg Clin North America—June, 1955)

in lowering portal hypertension and preventing esophageal hemorrhage Edwards has reviewed in a detailed manner venous collateral circulation and its efficacy resulting from portal obstruction [101] Experimentally, venous collateral circulation develops in about fifteen to twenty-five days [90]

Recently, venous catheterization and percutaneous transhepatic and transsplenic techniques have been introduced in an effort to secure indirect measurements of the pressures in the hepatic and

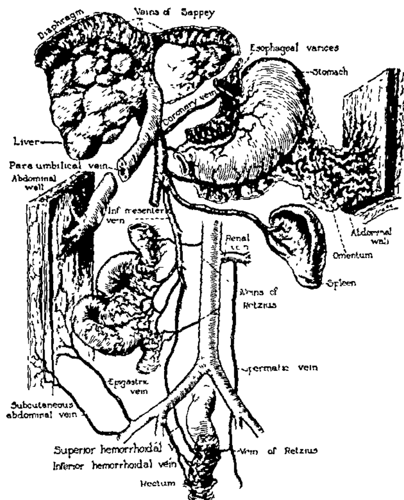


Fig 3a The venous collateral circulation occurring in cirrhosis, intrahepatic block of portal vein (Courtesy, McIndoe—Arch Path—January, 1928)

medusa" (Fig. 3a). Esophageal and gastric varices are ineffective large collateral veins between the portal and azygos venous systems (Fig. 3b). Linton has suggested that these varices are simply blunt ends of enlarged venous channels in the reservoir of the portal bed, because, infrequently, enlarged periesophageal veins connecting the esophagus with intercostal veins and the azygos system are found (Fig 4).[178] These naturally occurring shunts are ineffective

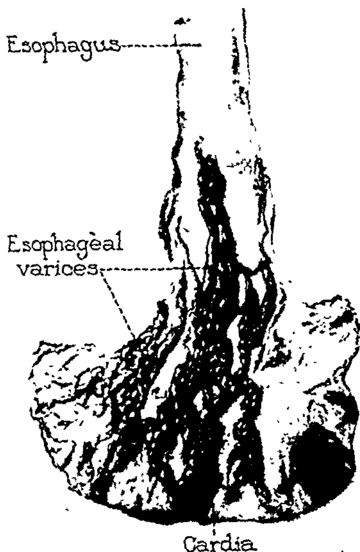


Fig 4 Injected specimen revealing esophagogastric varices (Courtesy, Mc-Indoe—Arch Path—January 1928)

portal veins These procedures appear useful in addition to splenoportal venography in estimating portal hypertension in distinguishing extrahepatic from intrahepatic portal block and in determining the efficacy of various shunt procedures in patients with cirrhosis The introduction of a cardiac catheter into the hepatic vein in humans and wedging this into a peripheral hepatic venule was described initially by Myers and Taylor and Friedman and Weiner in 1951 and has since been recommended by other investigators [50, 51, 63, 100, 116, 123, 170, 213, 235, 255, 257, 292, 313] The pressure obtained in the occluded hepatic venule has been termed the wedged hepatic venous pressure and correlates with the portal vein pressure. For the most part, wedged hepatic venous pressure is increased in at least half of the cirrhotic patients and more in those with demonstrable esophageal varices This pressure is independent of ascites and is lower after shunt procedures in patients with cirrhosis. Another method to determine portal venous pressure involves the technique of percutaneous hepatic venipuncture [9, 30, 31, 313] This procedure may immediately precede needle biopsy of the liver, the latter technique being necessary to establish the type of hepatic disease associated with portal hypertension Elevations in the portal venous pressure measured by transhepatic venipuncture have been observed consistently in cirrhosis, during the Valsalva procedure, and vomiting [220]

Another method of assessing portal venous pressure is the percutaneous measurement of intrasplenic pressure [11, 12, 78, 278, 294] This technique usually confirms with ease the existence of portal hypertension The disadvantages of the percutaneous venipuncture are that the risk, especially, of bleeding from the liver or spleen, may be appreciable, particularly in the absence of hepatosplenomegaly, and the determinations may be inaccurate due to arterial hypertension or ascites Only when employed concurrently with occlusive venous catheterization of the liver may the determinations of intrahepatic or intrasplenic pressures distinguish intrahepatic from extrahepatic portal hypertension [235, 313] For this reason, these techniques should also be employed simultaneously with venography The intrasplenic administration of iodinated serum albumin has been employed for the rapid measurement of hepatic blood flow and portal circulation times [253, 254] Direct measurement of the pres-

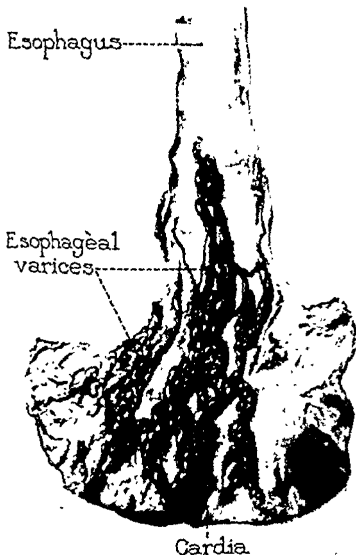


FIG 4 Injected specimen revealing esophagogastric varices (Courtesy, McIndoe—Arch Path — January, 1928)

sure within an esophageal varix during esophagoscopy has been recommended by Allison and Palmer, but is devoid of consistent accuracy and practicality in most hands.[4, 219] A metallic manometric tube 3 mm in width and 60 cm in length has been improvised which can be inserted through a 53 cm. Eder-Hufford flexible esophagoscope for direct measurement of venous pressure within an esophageal varix (Fig. 11). At the end of the tube is soldered a number 25 hypodermic needle The proximal end can be attached to a spinal fluid manometric set containing oxylated isotonic saline. I have noted, as have others, that there is no correlation between the severity and extent of esophageal varices, the esophageal variceal pressure, and portal venous pressures obtained surgically.[219] Finally, the determination of accurate portal venous pressure may be undertaken at the time of shunt operation using the portal vein or one of its larger tributaries. An ingenious instrument for this purpose employing a string-gauge manometer has been devised by Gray and his co-workers at the Mayo Clinic [129] Once esophageal varices are proved either radiologically or endoscopically, or by both techniques, it is necessary, whenever possible, to perform a needle biopsy of the liver in order to confirm the presence of cirrhosis. Esophageal varices are not pathognomonic of cirrhosis and, certainly, other conditions may give rise to portal hypertension [124, 227, 228, 246, 247, 282]

PATHOGENESIS OF PORTAL HYPERTENSION

The etiological classifications of various types of portal hypertension have been based upon the presence of esophageal varices and splenomegaly [54, 175, 247, 274, 316] A proposed etiological classification of portal hypertension is listed in Table I. In 1945 Whipple advocated a pathological classification of portal hypertension and separated this condition into two categories, in one the obstruction of the portal vein is intrahepatic and in the other the obstruction is extrahepatic.[307] Some classifications include various infiltrative hepatic diseases: amebic hepatitis, scleroderma, sarcoidosis, polycystic disease of the liver, fatty liver, metastatic neoplasm of the liver, hemosiderosis, and toxic and viral hepatitis as pathogenetic factors in the intrahepatic type of block [34, 77, 120, 168, 206, 222, 252, 276] Esophageal varices have been found by esophagoscopy and at

TABLE 1
CLASSIFICATION OF PORTAL HYPERTENSION

1 *Intrahepatic Type*
  - A Cirrhosis
  - B Schistosomiasis
  - C Neoplasm
  - D Congenital Narrowing of Portal Bed in Liver
  - E Intrahepatic Anomaly of Portal Radicals Anastomoses

2 *Extrahepatic Type*
  - A Thrombosis of the Portal and or Splenic Veins
  - B Cavernomatous Transformation of the Portal and or Splenic Vein
  - C Compression of the Portal and or Splenic Vein
    - 1 neoplasm
    - 2 [illegible]
  - D [illegible]
  - E [illegible]
  - F [illegible]

3 *Suprahepatic Type*
  - A Right Congestive Heart Failure
  - B Thrombosis of Hepatic Vein (Chiari's Syndrome)
  - C Compression of Hepatic and or Superior Vena Cava Veins
    - 1 neoplasm or lymphoma
    - 2 aortic aneurysm
  - D Chronic Constrictive Pericarditis

necropsy in several patients with fatty livers and massive necrosis of the liver. Undoubtedly, the most common cause of block of the portal vein in adults is cirrhosis, whereas in infants and children various types of extrahepatic lesions causing portal hypertension are observed more frequently [133 147 153] As a matter of fact, portal hypertension may exist without intrahepatic or extrahepatic portal block One patient was recently observed with congenital heart disease, microencephaly, diaphragmatic hernia, hepatosplenomegaly and hemorrhagic esophageal varices It was postulated that a splenic or hepatic arteriovenous fistula, or anomalies of the larger intrahepatic portal radicals might be responsible for portal hypertension

To recapitulate, the important clinical manifestations of portal hypertension on the basis of blockage of the portal vein in cirrhosis are esophagogastric varices, congestive splenomegaly with the syndrome of hypersplenism, hemorrhoids, thrombosis of the portal and/or splenic vein, Cruveilhier-Baumgarten syndrome, abdominal wall venous collaterals and possibly ascites Hemorrhagic erosive gastritis has been noted to be a complication of cirrhosis with portal hypertension [225,226] Porto-pulmonary anastomoses and decreased arterial saturation of the blood have been reported in cirrhosis and contribute to dyspnea commonly present in this condition [53 284] In

1882 Banti described a syndrome in which there were three stages and which was terminated by cirrhosis.[15-19] This syndrome does not exist as a specific clinical nor pathological entity as originally described and may be the result of various intrahepatic and extrahepatic causes of portal hypertension. Moschcowitz has coined the term "congestive splenomegaly" to explain the splenic manifestations of portal hypertension, the most important of which is hypersplenism (Chapter 7).[211-212] The pertinent morphological alterations of the spleen in this condition are splenic enlargement, hemorrhagic engorgement, fibroblastic transformation of the splenic pulp, perisplenitis, reduction in size of the malpighian bodies and fibrosis of the splenic sinuses. As a result, the reservoir function of the spleen is lost and this organ now has been converted to a closed venocapillary circuit. If pericutaneous manometric and hepatic vein catheterization techniques and esophagoscopy are employed routinely in any verified case of cirrhosis, it is reasonably certain the incidence of portal hypertension would increase over existing statistics. These statistics usually indicate that about one-third to one-half of patients with portal, postnecrotic, and biliary cirrhosis have portal hypertension.

Chiles and his co-workers at the Mayo Clinic demonstrated in a study of 80 cases of cirrhosis in which bleeding esophageal varices led to death that rupture of the varix was present in 39 per cent of the cases. This was due to increased hydrostatic pressure within the varix. Peptic ulceration of the varix was present in 50 per cent.[81] The routine therapeutic use of gastric antacids should be prescribed, therefore, for any patient with cirrhosis and esophageal varices.

DIAGNOSIS OF PORTAL HYPERTENSION IN CIRRHOSIS

A physical examination affords limited value in determining the presence of esophageal varices in the patient with cirrhosis. Neither does the severity of other stigmata of cirrhosis parallel the presence and severity of esophageal varices (Fig. 5). Brick and Palmer studied the clinical and esophagoscopic findings of 150 patients with cirrhosis, 95 of these (63.3 per cent) had endoscopic evidence of esophageal varices.[45, 49] Whereas the incidence of hepatosplenomegaly and ascites was unrelated to the presence of varices,

they found spider angioma in 62.1 per cent of their cases with varices and 29.1 per cent in those without varices.

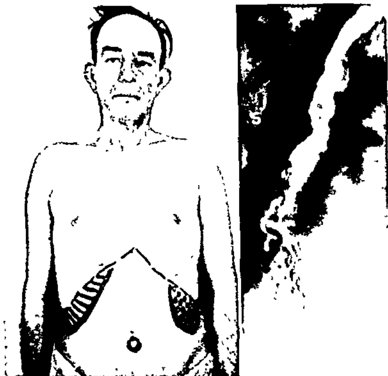


FIG. 5a. Patient with postnecrotic cirrhosis, probably due to exposure to carbon tetrachloride, and hypersplenism. Hepatosplenomegaly.
FIG. 5b. Roentgenogram of esophagus of the patient showing distal esophageal varices which had never hemorrhaged.

Radiological examination of the esophagus has not been generally effective as an accurate diagnostic procedure in determining the presence of esophageal varices. In many instances, this examination has been performed as part of a routine upper gastrointestinal roentgenologic examination. The thick tugal paste necessary to satisfactorily delineate esophageal varices has not been employed.[167] Brick and Palmer studied 248 patients proved by needle biopsy of the liver to have portal cirrhosis.[45] Esophageal varices

were found by roentgenologic examination in 39 cases (16 per cent) and by esophagogastric examination in 166 cases (69 per cent) Esophageal varices proven endoscopically in these cases were detected roentgenologically in only 23 per cent. In addition, these investigations found that no correlation existed between the size of the varix, the propensity toward hemorrhage, and the severity of portal hypertension In a personal series of 42 consecutive patients with established cirrhosis verified by needle biopsy of the liver, esophagoscopy revealed esophageal varices in 27 cases and *roentgenography, employing a thick barium paste, demonstrated* varices in 20 cases The use of the latter medium for an esophagogram and careful technique of the roentgenologist will increase the radiological detection of varices [122,167]

Routine esophagoscopy, preferably employing a flexible-tip telescopic esophagoscope, 53 cm. in length, is suggested in any patient with cirrhosis proved by needle biopsy of the liver (Fig 6). This procedure is remarkably safe and can be performed with ease by the experienced endoscopist on ambulatory patients After the administration of a topical buccal and pharyngeal anesthesia, the operator may easily visualize the entire esophagus with reasonable precaution and accuracy within several minutes (Fig. 7). Simultaneous manometric readings of the venous pressure within esophageal varix may also be attempted with facility, although the benefit from this technique, if any, would appear to be the comparison of pressures before and after a shunt procedure In fact, annual esophagoscopies are advisable in order to demonstrate the appearance or disappearance of esophageal varices for any patient with established cirrhosis, even those who adhere to a strict medical therapeutic program. The natural history of esophageal varices secondary to portal cirrhosis has been assessed, and it has been determined that varices from time to time vary in diameter and extent They tend to improve as the general clinical course improves, and to worsen as the clinical course worsens [209,224,229] Bennett has called attention *to 5 of 12 patients with cirrhosis treated medically in* whom there was spontaneous endoscopic disappearance of esophageal varices [25] Three alcoholics with fatty portal cirrhosis were observed, and esophageal varices were noted to disappear within thirteen, eighteen, and twenty-three months, respectively In the second

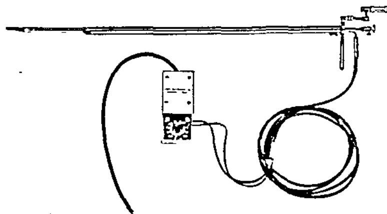


FIG. 6a A diagnostic flexible tip esophagoscope (Eder Hufford), 53 cm in length and accessories

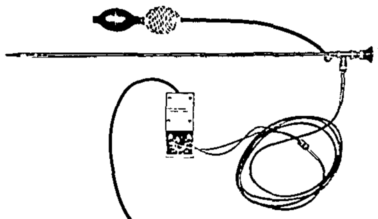


FIG 6b A diagnostic, rigid gastroscope or funduscope (Eder Palmer) which can be inserted in this esophagoscope, following its routine introduction, to visualize gastric varices (Courtesy, Streifeneder, L.)

were found by roentgenologic examination in 39 cases (16 per cent) and by esophagogastric examination in 166 cases (69 per cent). Esophageal varices proven endoscopically in these cases were detected roentgenologically in only 23 per cent. In addition, these investigations found that no correlation existed between the size of the varix, the propensity toward hemorrhage, and the severity of portal hypertension In a personal series of 42 consecutive patients with established cirrhosis verified by needle biopsy of the liver, esophagoscopy revealed esophageal varices in 27 cases and roentgenography, employing a thick barium paste, demonstrated varices in 20 cases The use of the latter medium for an esophagogram and careful technique of the roentgenologist will increase the radiological detection of varices.[122,167]

Routine esophagoscopy, preferably employing a flexible-tip telescopic esophagoscope, 53 cm in length, is suggested in any patient with cirrhosis proved by needle biopsy of the liver (Fig. 6). This procedure is remarkably safe and can be performed with ease by the experienced endoscopist on ambulatory patients After the administration of a topical buccal and pharyngeal anesthesia, the operator may easily visualize the entire esophagus with reasonable precaution and accuracy within several minutes (Fig 7). Simultaneous manometric readings of the venous pressure within esophageal varix may also be attempted with facility, although the benefit from this technique, if any, would appear to be the comparison of pressures before and after a shunt procedure In fact, annual esophagoscopies are advisable in order to demonstrate the appearance or disappearance of esophageal varices for any patient with established cirrhosis, even those who adhere to a strict medical therapeutic program The natural history of esophageal varices secondary to portal cirrhosis has been assessed, and it has been determined that varices from time to time vary in diameter and extent. They tend to improve as the general clinical course improves, and to worsen as the clinical course worsens [209,221,229] Bennett has called attention to 5 of 12 patients with cirrhosis treated medically in

teen, eighteen, and twenty-three months, respectively. In the second

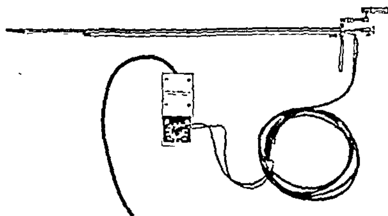


FIG. 6a A diagnostic, flexible tip esophagoscope (Eder Hufford), 53 cm in length and accessories

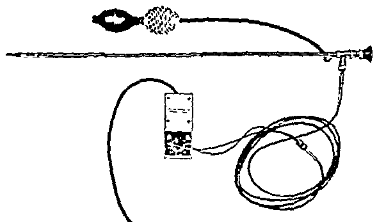


FIG. 6b A diagnostic, rigid gastroscope or funduscope (Eder Palmer) which can be inserted in this esophagoscope, following its routine introduction, to visualize gastric varices (Courtesy, Streifeneder, L.)

patient, ascites, edema and jaundice also disappeared and there was marked improvement in the hepatic function tests within this period of time.

More frequent emergency and routine use of flexible telescopic esophagoscopy to verify the presence of esophageal varices in cases of massive upper gastrointestinal hemorrhage is important, particularly, in patients without physical stigmata of cirrhosis.[47,55,81,218,319,320] This dictum has saved the lives of 3 patients recently. In one, the physical findings and hepatic function tests did not suggest cirrhosis. The emergency use of flexible esophagoscopy can be performed with the patient in bed and, perhaps, is the only exception to the rule that this technique should be preceded by an esophagogram for safety. A rigid gastroscope such as the Eder-Palmer fundoscope may be inserted into an Eder-Hufford telescopic esophagoscope if necessary to visualize gastric varices (Fig. 6b). An esophagogram, nevertheless, should always be ordered before such esophagoscopy, and endoscopic indications, contraindications, and inherent dangers should always be appreciated.[233]

In cases of indeterminate massive hematemesis, the most common source of the bleeding is duodenal or gastric ulcer. Even if an esophagogram or esophagoscopy reveal esophageal varices, this finding should not necessarily be considered the exact source of the hemorrhage. The frequent concurrence of other hemorrhagic lesions in the upper gastrointestinal tract occurring in cirrhotics has been reported by observers. Duodenal ulcer, gastric varices, gastric ulcer, hemorrhagic gastritis, hiatal hernia, lacerations of the gastroesophageal junction (Mallory-Weiss syndrome), esophagitis, and neoplasm may also be responsible for gastrointestinal hemorrhage in patients with cirrhosis and esophageal varices.[47,110,113,143,153,154,158,226,227,244,279,281] Palmer and Brick emphatically warn against the presumptive diagnosis of bleeding esophageal varices in cirrhotics despite their known presence.[226] They found that in 39 per cent of 95 patients with upper gastrointestinal hemorrhage, cirrhosis and esophageal varices, additional lesions of the upper gastrointestinal tract in addition to varices could have been responsible for hemorrhage. Duodenal ulcer was found in 10 per cent of their patients. Along this line, it may be advisable to determine the



Fig. 7. Enlarged esophageal varices which were reproduced through a diagnostic esophagoscope in a patient with postnecrotic cirrhosis.

amounts of blood pepsin and ammonia in patients with upper gastrointestinal hemorrhage and cirrhosis.[198] Elevated levels of blood pepsin generally occur in duodenal ulcer.[276] Palmer calls attention to the presence of esophageal varices in the absence of portal hypertension and cirrhosis.[227] Thirteen such patients (3.7 per cent) selected from 350 cases with endoscopically proven esophageal varices were reported, and 9 of the 13 had hemorrhaged.

In addition to esophagoscopy, an emergency bromsulfalein test may also afford diagnostic aid in determining the source of an upper gastrointestinal hemorrhage. Zamcheck has reported that retention of this dye usually was present in patients with cirrhosis and hemorrhagic varices, and only occasionally was there abnormal retention in with hemorrhagic duodenal or gastric ulcer.[321] Finally, as soon as possible, all patients with massive upper gastrointestinal hemorrhage should have a roentgenogram of the upper gastrointestinal tract. In the event that slow oozing persists or hemorrhage has stopped within twenty four to forty-eight hours, fluoroscopy without palpation (Hampton technique) may be recommended to discern a hemorrhagic lesion.[134]

Transsplenic, direct portal and transhepatic venography are exceedingly useful and practical roentgenological diagnostic procedures to visualize the portal vein and its tributaries. These techniques are important in determining the extent and distribution of collateral circulation in a patient with an enlarged spleen, the extent of invasion of neoplasms of the liver, pancreas, or adjacent areas, in distinguishing intrahepatic from extrahepatic portal block, and to visualize the portal and splenic veins prior to surgical correction of portal hypertension. For these reasons, if possible, splenoportal venography should be performed routinely in any patient with portal hypertension.

The most practical type of preoperative splenoportal venography is the transsplenic technique (Fig. 8). The details of this procedure have been discussed in several reports.[1,2,10,43,56,60,83,91,92,114,116,146,155,203,217,259,260,263,297] After excluding hypersensitivity of the radiopaque iodine dye by a minute intracutaneous or intravenous injection, this substance in amounts varying from 30 to 50 cc. (70 per cent sodium acetrizoate—Urokon, 70 per cent iodopyracet—



FIG 8a Percutaneous splenoportogram filmed at eleven seconds demonstrating the tortuous, distended portosystemic veins, particularly the coronary vein, gastric and esophageal varices, and also the anastomosis between the inferior mesenteric vein and the superior hemorrhoidal plexus as observed generally in portal hypertension

Diodrast; or 70 per cent sodium iodomethamate—Neo-Iopax) is injected meticulously but rapidly into the spleen in the left ninth interspace slightly cephaled Immediately, roentgenograms are then made at intervals of one to two seconds (Fig. 9) The risk of this procedure to the patient particularly in the hands of the neophyte are splenic tear, intraabdominal hemorrhage, and severe pain. Some investigators apparently feel that transsplenic venography can be performed in the ambulatory patie

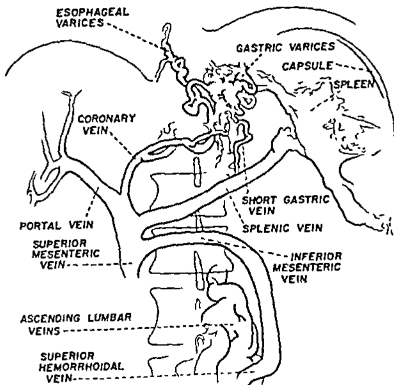


FIG. 8b Diagrammatic illustration of Figure 8a (Courtesy, Evans, J. A. and O'Sullivan, M. D.—M. Radiog. & Photog.—1955.)

tion should be taken lightly. One is impressed that the procedure is performed best in the hands of an experienced general surgeon in the operating room where an emergency splenectomy may be performed, if necessary, and immediate resuscitative measures are readily available. Atkinson and Sherlock in 1955 reported no fatality from this technique in their wide experience and from nearly 400 cases reported in the literature.[10] De Almeida performed 117 percutaneous splenic splenoportographies on 112 patients with only one fatality.[79] Du Boulay and Green observed 5 patients at laparotomy with portal hypertension upon whom direct splenic venography was performed.[94] They noted hemorrhage in the

amount of 50 to 200 cc of blood from the splenic puncture wound Apparently, in careful hands the incidence of splenic hemorrhage is appreciably small The contraindications of splenoportography are similar to those of needle biopsy of the liver.

Splenoportal venograms may also be performed by direct injection of radiopaque dye into the portal vein or its tributary at the time of laparotomy (Fig 10) [35,69,173,305] This route is less practical



than the transsplenic route, which affords more significant preoperative diagnostic information. Dreyer has found direct portal venography inadequate because the injection of radiopaque dye into a hypertensive portal system impairs the quality of the venogram.[91] Additional, though less adequate, methods of venography include direct injection into a venous collateral on the anterior abdominal wall, splanchnic arteriography and the technique employing the saphenous vein. It has been noted that neoplastic extrahepatic portal hypertension may be confirmed by combining the techniques of percutaneous transsplenic splenoportography and abdominal aortography. Finally, transhepatic venography has been described by Bierman and co-workers.[30 31] This may be performed simultaneously with transhepatic venule or hepatic vein catheterization.[172 235 313] This roentgenological procedure is said to be more safe and less complicated than the transsplenic technique. In addition, the transhepatic technique may be employed for hepatic arteriography in addition to venography. Costal intraosseous venography has been described as an alternate venographic method.[273]

TREATMENT OF PORTAL HYPERTENSION IN CIRRHOSIS

The therapeutic management of portal hypertension in patients with cirrhosis is directed primarily toward the control of bleeding esophagogastric varices and the correction of marked hypersplenism. In order to select the proper corrective therapy of these conditions in patients with cirrhosis, it is imperative that treatment be classified as either a medical or surgical emergency or elective surgical. For all practical purposes the treatment of hypersplenism is always elective, whereas management of bleeding esophageal varices is either elective or emergency. In selecting the type of management for bleeding esophageal varices in patients with cirrhosis, it is mandatory to recognize the frequent association

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←

FIG. 9a. Percutaneous splenoportogram showing obstruction of the portal and splenic veins. Esophagoscopic examination was normal, however, gastroscopic examination revealed marked congestion and edema of the gastric rugae and multiple varices along the lesser curvature, neoplastic, probably pancreatic, extrahepatic portal hypertension. (Kleckner, M. S., Jr.—Bull. Am. Gastroscopic Soc.—December, 1955.)

amount of 50 to 200 cc. of blood from the splenic puncture wound Apparently, in careful hands the incidence of splenic hemorrhage is appreciably small The contraindications of splenoportography are similar to those of needle biopsy of the liver.

Splenoportal venograms may also be performed by direct injection of radiopaque dye into the portal vein or its tributary at the time of laparotomy (Fig 10) [38,60,173,303] This route is less practical



called attention to the fact that these original statistics may not reflect the prognosis of the patient with cirrhosis nowadays principally because of the greater use of blood transfusions, antibiotics, esophageal balloon tamponade and strict medical management.[215] Inadequate or hasty preoperative preparation of cirrhotic patients for eventual elective surgical decompression will increase the usual incidence of postoperative mortality

EMERGENCY MEDICAL TREATMENT OF ESOPHAGEAL VARICES

The treatment of massive gastrointestinal hemorrhage in patients with cirrhosis who are bleeding from esophageal varices consists of first, the control of hemorrhagic shock (Table II) This includes the transfusion of sufficient amounts of correctly typed and crossed matched whole blood, if available, or type O blood, or a plasma expanding agent such as dextran, gelatin, human albumin, and, lastly, plasma. In addition, the patient should be administered oxygen, antibiotics, and sedation and other supportive measures as

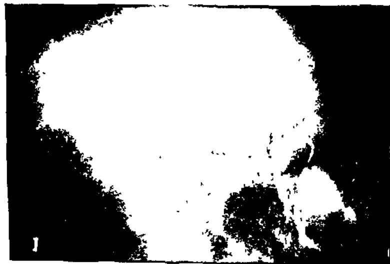


Fig. 10. O[illegible]

coronary veins

of or termination in hepatic insufficiency and ascites It has been reported that from 50 to 80 per cent of patients with cirrhosis and esophageal varices die within one year of their first gastrointestinal hemorrhage[67, 89, 119, 250, 283] Nachlas, O'Neil and Campbell in 1955



Fig 9b Abdominal aortogram of the same case showing normal appearance of the abdominal aorta and tributaries. (Kleckner, M S, Jr —Bull Am Gastroscopic Soc —December, 1955)

0	0	0	0	0	0	0	0	0	0	0	+
0	0	0	0	0	0	0	0	0	0	0	0
+	+	+	0	0	0	0	0	0	0	0	+
+	+	+	+	+	+	+	+	‡	+	0	0
0	0	0	0	0	0	0	0	0	0	0	+
+	0	0	0	0	0	0	0	0	0	0	0
74/50	102 68	136 86	126 81	normal	→						
0	+	+	0	0	0	+	‡	0	0	0	0
0.5/4.5		0.8/3.3			0.8/1.6			1.1/3.6			1.6/2.9
21								27			45
34		3+			2+			2+			2+
8.0					11.9			10.8			13.5
12.7		23.2			21.3			21.5			15.5
					32			18.5			
					83			193			
5.3	13.9				14.2		13.9	13.5		14.2	13.0
19	43				46		45	43		46	41
3.0					2.7			2.5			3.5
2.9					4.0			3.6			4.0
45					42		44	42			50
3000	1000	500			1500						

Ambulatory dismissal — ← Esophageal Tamponade → — ↑ Portacaval shunt — ↑ Ambulatory Dismissal

20 22 24 26 28 30 32 34 36 38 40 42 44 46

estimate of hematemesis, and the progress of and the effect of tilting on the patient's blood pressure and pulse. The use of a head-up tilt test performed at the patient's bedside has been recommended in determining blood loss and detecting impending shock from gastrointestinal hemorrhage.[151,304] The usual laboratory and clinical procedures employed for evaluating blood loss due to hemorrhage may be misleading and measurements of plasma and blood volumes are particularly useful aids.[72,94,184,238,239,259,307,317,318] Accurate loss of blood may be measured by simultaneous and serial blood volume determination employing high molecular weight dextran or Cr^{51}-labeled erythrocytes and I^{131}-labeled albumin.[44,60]

TABLE II

Clinical Course of a 62 Year old Patient with Portal Cirrhosis and Repeated Esophageal Hemorrhages Due to Esophageal Varices, Serum Hepatitis Developed in Late Clinical Course

Clinical Findings										
Enlarged liver	0	0			0	0	0	0	0	0
Enlarged spleen	0	0			0	0	0	0	0	0
Jaundice	0	0			0	0	+	+	+	0
Ascites	0	0			0	0	+	+	+	+
Edema	0	0			+	0	+	+	+	+
Eesophageal hemorrhage					+	0	0	0	0	0
Blood pressure	70/50	70/50			60/40	125/70	←	normal		→
Prehepatic coma	0	0			0	0	+	0	0	0
Laboratory Tests										
Bilirubin, serum, per 100 cc		0 2 / 2 2					1 4 / 4 1		1 0 / 3 4	
BSP Retention 45 min		21					40		28	
Cephalin flocculation		2+							14	
Thymol turbidity		6					8 1		9 7	
Zinc sulfate turbidity		22 9								
Serum mucoprotein										
Serum iron										
Hemoglobin, gm/100 cc	8 5	8 5	13 1		15 5		12 3		11 7	11 2
Hematocrit	27	27	41		48		40		39	37
Albumin serum, gm/100 cc.		3 3					3.2		2 3	
Gloubin, serum, gm/100 cc		2 3					3 0		4 1	
Prothrombin time %	50	50			39		39		41	45
Treatment										
Blood transfusion, cc		6500			1500					
Operation		←	Esophageal Tamponade	→	↑ Transesophageal Ligation of veins					
Days		*0*	*2*	*4*	*6*	*8*	*10*	*12*	*14*	*16*

the Fowler position should be employed. Indiscriminate emergency use of narcotics or sedative drugs should be avoided These drugs should be reserved solely for those patients with unusual anxiety. Phenobarbital is a particularly safe sedative and hypnotic because it is excreted largely by the kidney An antibiotic combination such as *penicillin and dihydro-streptomycin is also recommended* in this condition because intercurrent infections or impending hepatic failure may occur following hemorrhage The estimation of the amount of blood required to transfuse these patients may be calculated by the determination of the blood and plasma volume, the hematocrit and hemoglobin of the blood, an

Electrolyte and liver function values in a patient with portal cirrhosis, bleeding esophageal varices, ascites, and hepatic coma

	6-20	6-23	6-27	7-4	7-6
Serum Albumin (3.6–5.4) Gm./100 cc.	1.9	—	1.2	—	
Serum Globulin (1.9–3.4) Gm./100 cc.	4.0	—	4.2	—	
Bilirubin (0.2–1.0) mg./100cc	2.08/6.70	—	3.5/11.0	4.75/11.52	
B.U.N. (10–18) mg./100cc	14	10	7	15	22
CO_2-Capacity (22–31) mM/L.	22	27	24	24	19
Chloride (99–111) mEq/L.	105	102	98	77	71
Sodium (137–143) mEq/L.	132	128	133	110	115
Potassium (4–5) mEq/L.	4.5	4.2	4.0	3.5	4.5
BSP (0–5) 45	45	—	—	—	—
Ceph. Floc. (0–2+)	4+	—	—	4+	—
Thymol Turbidity (0–7)	10.5	—	—	12.0	—
	hematemesis 1000cc; esophageal tamponade; 1500 cc blood transfusion	6000 cc. Paracentesis		deep hepatic coma; daily 3% NaCl I.V.	death

Fig. 12

[24, 160, 168, 179, 224, 225a, 277, 315] The triple-lumen tube, preferably with a double rather than a single balloon for additional tamponade of the gastric aperature, has been used diagnostically to ascertain the source of the upper gastrointestinal bleeding [32, 151, 293] An adult and child-sized esophageal balloon has been manufactured (Fig. 12) A reduction in mortality from about 80 to 50 per cent through the use of esophageal balloon tamponade has occurred in esophageal variceal hemorrhage So important are the therapeutic indications of the esophagogastric balloon that I have included herein the instructions for passing it according to Sengstaken's technique [277]

Instructions for Passing the Sengstaken Esophageal Balloon for the Control of Bleeding From Esophageal Varices

Equipment Needed

1 Esophageal varices tube with balloons

2 Mercury manometer or Aneroid gauge of the Tycos sphygmomanometer to be connected with a "Y" glass tube to upper sausage balloon

[69, 163, 205, 268] The successful management of
rhage depe...
per ... is advocated

... effective emergency method of controlling esophageal hemorrhage has been esophageal tamponade with a balloon, first introduced by Rowntree and co-workers in 1947.[267] This technique has become a standard emergency measure and should always be employed primarily in cases of verified hemorrhagic esophageal varices Discontinuous gastric suction via the gastric lumen of the tube may afford additional information if the hemorrhage is gastric or duodenal in origin Three types of balloons used are the Sengstaken and Blakemore, Patton and Johnston, and Nachlas[19]

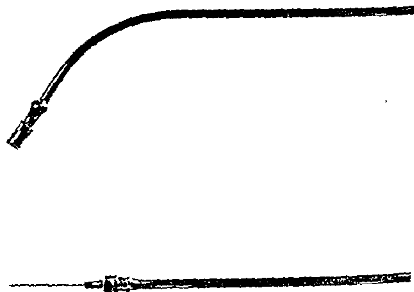


Fig 11a (*Upper*, distal end) (*Lower*, proximal ...

hour This will help prevent the tube from being clogged with blood clot The stomach must never be allowed to fill as the patient will then regurgitate the tube. Keeping the head of the bed elevated also helps keep the stomach empty This also helps to decrease nausea and gagging Adequate sedation is absolutely essential Regurgitation is due to two causes usually, the most important of which is lack of sedation, the other is allowing the stomach to become filled. Bleeding should be stopped and the stomach can be kept free of blood once adequate pressure is maintained upon the esophageal wall If the tube should be regurgitated, it should be re passed immediately without hesitation

6 The tube with the balloon inflated should be kept at the minimal pressure required to control bleeding, approximately 25 mm of mercury for at least forty-eight hours and then deflated for twelve to twenty-four hours to see if new bleeding occurs If none occurs then the balloon may be slowly withdrawn with very little danger of starting new bleeding During the time that the balloon is in place, the patient must be kept hydrated and can be given some nutrition by intravenous or clysis fluids. Feedings can be given through the stomach part of the tube, 100 to 150 cc hour, with the head of the bed elevated and the patient on his right side. If all goes well, the stomach may be aspirated just before feedings Feedings which are too bulky must be avoided as they will clog the tube and remain in the stomach an undue length of time It must be remembered that placing too much food within the stomach will increase the dangers of vomiting the tube and therefore extreme caution must be used for there is great variability in the tolerance of patients In cases requiring prolonged tamponade, tube feedings are more important.

7 It is important to emphasize that the patient is to swallow nothing, not even saliva, once the tube is in place In cases having excessive accumulation of mucus, the balloon may be deflated for a few minutes several times a day

8 After the tube has been withdrawn, the patient may be started on clear liquids and slowly advanced to a soft diet

9 If, after the esophageal balloon is inflated to as much as 30 to 35 mm of mercury, repeated aspirations from the stomach reveal bright red blood, it usually means the source of bleeding is from a coronary vein on the stomach wall, a rare occurrence in our experiences In this event, the patient is given additional

3 A 50 cc syringe
4 Constant intestinal suction machine (Gomco).
5 Lubricating jelly (not vaseline).
6 Glass of water with straw
7 One clamp for rubber tubing such as a Crile, Kelly, or Kocher hemostat.

Instructions for Passing the Tube

1 Coat the lower part of the tube and the balloon with a thin coat of lubricating jelly and pass the tube through the nostril until the tip is in the posterior pharynx or throat Then, with swallows of water sipped through the straw in the glass of water, pass the tube to at least the 50 cm. mark.

2 Next, inflate lower balloon with 150 to 200 cc. of air, withdraw tube slightly until resistance is encountered Then, inflate upper sausage balloon to 20 mm of mercury pressure and finally tape tube to nose securely

3 Next, aspirate the stomach such that all of the blood is out of the stomach as well as air and swallowed water During the aspiration, it is advisable to irrigate the tube frequently with at least 10 cc of water to prevent the tube from clogging due to blood clotting

4 Adjust pressure in upper balloon until bleeding ceases as determined by aspiration, usually 20 to 25 mm of mercury as read on the manometer connected to one branch of the glass "Y" tube When the balloon is in the proper position, the pressure will vary with cardiac and respiration pulsations and with contractions of the esophagus which may raise the pressure to 70 mm of mercury The pressure should not fall much below the abovementioned pressure. This pressure will require approximately 40 to 60 cc. of air If more than this amount of air is needed to give an adequate pressure (*viz.*, 200 cc.) one may be fairly certain that the balloon is well out of the esophagus and into the stomach and hence down too far After sufficient air is placed within the balloon, securely clamp the branch of the "Y" tube that was used to inflate the balloon so that it will not leak air Check the pressure frequently to be sure that no leakage has occurred A portable x-ray may be taken at this point to check the position of the tube.

5. Then connect the stomach aspiration tube to constant suction, irrigating the tube with 40 cc of warm saline every half

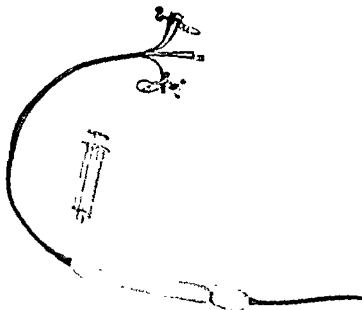


FIG 15 Conventional adult size Sengstaken, triple lumen nasogastric tube and esophagogastric balloons for variceal tamponade (Courtesy, Medical Press, Inc)

topical thrombin or U. S. P (oxycel) gauze administered orally or esophagoscopically

EMERGENCY SURGICAL TREATMENT OF ESOPHAGEAL VARICES

In the event that emergency medical management of hemorrhagic esophageal varices is unsuccessful, there are several emergency surgical methods that have been employed These procedures have less post-operative risk than shunt procedures, but are temporarily effective. These consist of. (1) transesophageal ligation of esophageal varices, (2) partial esophagogastrectomy, (3) ligation of coronary and gastric veins and splenic artery, (4) posterior

sedative at once, the nasogastric tube is snubbed up firmly and taped securely to the nose. Finally, the stomach balloon is inflated with more air gradually, to avoid retching. It may require a total of 300 to 400 cc of air to arrest bleeding.

Brunjes has devised a simple apparatus for maintaining constant pressure in an esophageal balloon, and Wallace and his co-workers have recommended a head-mask to maintain the balloon in a stationary position.[52,301] Infrequent complications attending the use of esophageal balloon are posterior pharyngeal obstruction, esophageal rupture, aspiration pneumonitis, ulceration of the esophagus, failure of the esophageal and gastric balloon to deflate, nausea and vomiting, and passage of the tube into the stomach.[19,24,166,256,311] Successful use of esophageal tamponade largely depends upon experienced manipulation and careful decompression of the balloon in twenty-four to forty-eight hours, if possible, and removal of the tube in forty-eight to seventy-two hours. Esophageal balloon tamponade should be used to control bleeding esophagogastric varices only in emergency situations. Within several weeks definitive surgical portal decompression should be considered.

Prompt institution of esophageal tamponade for esophageal variceal hemorrhage is important. Procrastination or inexperience in balloon-tamponade is a risk to the patient of a repeated bout of uncontrollable hematemesis. As a result, once delayed tamponade is instituted, the patient succumbs to hepatic insufficiency as the consequence of severe hepatic anoxia due to hemorrhagic shock superimposed on an already badly diseased liver. In 31 consecutive personal cases of cirrhosis, esophageal tamponade was effective in controlling hemorrhage due to bleeding esophageal varices in every instance except two. However, fatal hepatic coma occurred in 16 instances, and in 1 case this was considered to be aggravated by an aspiration (blood) pneumonitis. Blakemore also noted that the recovery rate from esophageal variceal hemorrhage was 50 per cent greater in patients who had esophageal tamponade instituted at the same time as blood transfusions.[37,39] It is necessary for every hospital to have available for emergency use a tray which contains the necessary equipment for esophageal balloon tamponade. In its absence, occasionally, clot formation may be induced by the use of

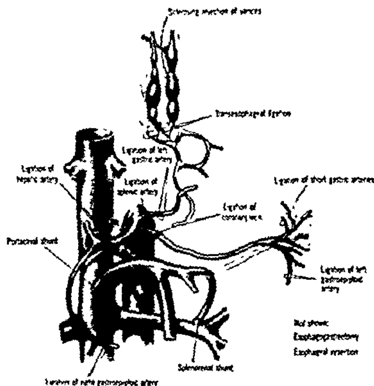


Fig. 14 Various operative procedures to control bleeding esophageal varices (Courtesy, Medical Press, Inc.)

terial ligation, however, are favorable results accrued by splenectomy

Posterior mediastinotomy as recommended by Som and Garlock in a manner similar to the concept of the Talma-Morison omentopexy was proposed in order to increase the venous collateral circulation between the esophagus, mediastinum, and chest wall [283,290] These authors claim that portal blood can then be returned to the systemic circulation by the azygos veins The operation con-

mediastinotomy; (5) endoscopic sclerosis of esophageal varices and coronary veins; and (6) splenectomy (Table IV) (Fig. 14).

Transpleural transesophageal ligation of bleeding esophageal varices was first described by Boerema in 1949 and Crile in 1950; and a transabdominal technique was described by Welch in 1956 [42 TO 310] The successful results obtained by this procedure indicate that it is only temporarily effective (several weeks) in aborting further variceal hemorrhage. However, it is probably the most effective type of emergency surgical measure for this condition. Nevertheless, infection or delayed wound healing, due to hypoproteinemia or hypersplenism in an unprepared cirrhotic increases the morbidity of this procedure.

Partial esophagogastrectomy for hemorrhagic esophageal and gastric varices has been recommended by Phemister and Humphreys in 1947 and others (Fig. 15).[41,130,189 216 241 262 303 304 318] Surgical resection of the lower esophagus and cardiac area of the stomach removes the source of the hemorrhage. The main objections of this method are the appreciable postoperative mortality, failure to correct the portal hypertension, and gastric atony due to vagotomy. In the case of the latter complication a gastroenterostomy may be indicated. Cooley and DeBakey have proposed an extensive subtotal resection of the esophagus as definitive treatment for bleeding esophageal varices.[65]

Ligation of the coronary and gastric veins to reduce portal pressure in the esophagogastric region and ligation of the splenic artery in order to reduce the arterial blood flow into the hypertensive portal vein have been recommended as emergency surgical measures in cirrhotics with hemorrhagic esophageal varices.[33,93 145 177-191,302] Linton has found these procedures ineffective and has abandoned their use in his clinic.[178] Inadequate portal venous decompression, recurrent esophageal hemorrhage, postoperative mortality, thrombosis of the splenic or portal veins, postoperative intra-abdominal hemorrhage from collateral veins, and eventual hepatic insufficiency affect the theoretical benefits derived from these procedures. Obliteration of hypersplenism and partial reduction of portal hypertension eliminating 20 to 40 per cent of the total amount of arterial blood entering the portal vein by splenic ar-

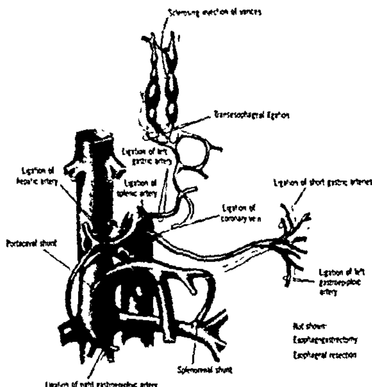


Fig 11 Various operative procedures to control bleeding esophageal varices (Courtesy, Medical Press, Inc)

terial ligation, however, are favorable results accrued by splenectomy

Posterior mediastinotomy as recommended by Som and Garlock in a manner similar to the concept of the Talma Morison omentopexy was proposed in order to increase the venous collateral circulation between the esophagus, mediastinum, and chest wall [295,290] These authors claim that portal blood can then be returned to the systemic circulation by the azygos veins The operation con-

sists in packing the superior mediastinum with a long piece of gauze through a supraclavicular incision This foreign body is removed, thus gradually promoting the formation of granulation tissue. However, this procedure has not been accepted because, as Linton states, the type of venous bypass is ineffective.

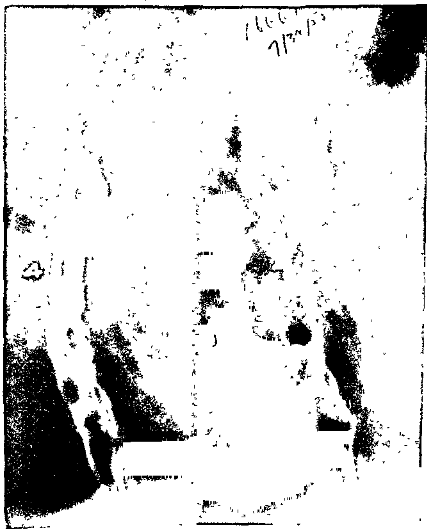


FIG 15a Roentgenograms of the esophagus from a patient with posthepatitic portal cirrhosis showing extensive esophageal varices The patient also hemorrhaged from esophageal varices after a splenorenal shunt had been performed nearly a year previously

Endoscopic sclerosis of esophageal varices as definitive treatment was first proposed by Crafoord and Freuchner in Sweden in 1939.[65] More recent optimistic reports are those, respectively, of

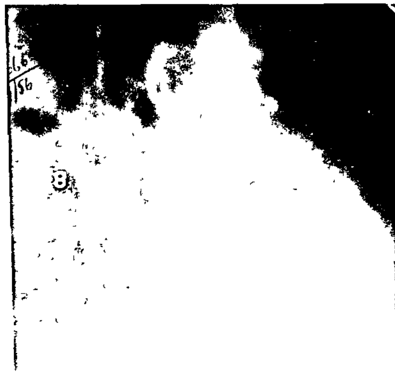


FIG. 15b. Roentgenogram of esophagus of same patient after eventual partial esophagogastrectomy. Esophageal varices were absent radiologically and esophagoscopically three months postoperatively.

sists in packing the superior mediastinum with a long piece of gauze through a supraclavicular incision This foreign body is removed, thus gradually promoting the formation of granulation tissue. However, this procedure has not been accepted because, as Linton states, the type of venous bypass is ineffective.



Fig 15a Roentgenograms of the esophagus from a patient with posthepatic portal cirrhosis showing extensive esophageal varices. The patient also hemorrhaged from esophageal varices after a splenorenal shunt had been performed nearly a year previously

of three should be advocated. Therapeutic measures should also be instituted to combat ulceration of esophageal varices. The high incidence of ulcerated hemorrhagic esophageal varices, concurrence of duodenal ulcer and, therefore, gastric hyperacidity and regurgitation of acid into the esophagus due to an esophagogastric insufficiency compels the therapeutic administration of gastric antacids and bland dietary features similar to ambulatory ulcer diets for patients with cirrhosis and esophageal varices. Baronofsky and Wangensteen suggest that portal and splenic vein obstruction abets the ulcer diathesis.[20, 21, 303, 304] A 95 to 98 per cent gastric resection has been proposed by them for the treatment of portal hypertension in order to eliminate gastric secretion and also, when combined with splenectomy, to reduce portal hypertension.

ELECTIVE SURGICAL TREATMENT OF ESOPHAGEAL VARICES

This category includes those surgical procedures which shunt blood from the portal vein into the systemic circulation and which constitute, generally, the most effective treatment of portal hypertension in patients with cirrhosis. These operations are (1) portacaval shunt, (2) splenorenal shunt, (3) superior mesenteric-caval shunt, and (4) the inferior mesenteric-ovarian shunt (Tables III, V) (Fig. 16). The first two shunt procedures are most generally employed. The first report of a portacaval shunt was that of Eck, a Russian physiologist in 1877.[99, 174, 262, 263] He shunted blood from the portal vein to the inferior vena cava in experimental animals, a procedure thereafter called an Eck fistula. A historical summary of the various portal to systemic venous shunt procedures collected from the reports of Whipple and Baronofsky, respectively, is arranged in Table IV.[20, 316] In 1945 Whipple and Blakemore demonstrated that a shunt for the surgical treatment of portal hypertension in patients with cirrhosis was safe and effective.[34, 316] Before that time these methods were generally ineffective because they were employed also for ascites, or preoperative treatment and selection of patients was inadequate. Before the technique and results of these shunt procedures are discussed, it is necessary to consider operative criteria, selection, and necessary preoperative preparation of cirrhotic patients with esophageal varices. In selecting a patient

Moersch, Patterson, and Welt.[208,236,237,314] Grace in 1912 attempted surgical sclerosis and ligation of the coronary veins.[128] These procedures have been considered ineffective in most hands, because portal hypertension is uncontrolled, gastric varices escape sclerosis, and further bleeding may ensue McBeth considers this method a safe and satisfactory alternative to major surgery and recommends esophagoscopy twice yearly in patients with cirrhosis in order to visualize new esophageal varices[195] Two per cent sodium morrhuate has been employed as the sclerosing agent.

ELECTIVE MEDICAL TREATMENT OF ESOPHAGEAL VARICES

This therapeutic regimen is directed toward the dietary management of esophageal varices and control of reflux of gastric hydrochloric acid as the result of esophagocardiac insufficiency. It should not supplant the surgical treatment of esophageal varices and is invariably employed in patients with cirrhosis whose esophageal varices have not bled Even so, in some clinics the elective medical management of esophageal varices that have not bled has not been advocated.[157] Palmer and Brick have also recommended treatment of non-bleeding esophageal varices by shunt procedures because many of these patients eventually hemorrhage.[230] On the other hand, Bennett and co-workers have demonstrated endoscopically that esophageal varices may disappear after prolonged institution of a medical program[25] This should include a high-caloric, high-protein, high-carbohydrate and moderate-fat diet and abstinence from alcohol[96] The appreciation of this unusual phenomenon can be gained only through the routine use of esophagoscopy in every patient having cirrhosis

Other elective medical measures recommended in the management of esophageal varices are reduction of obesity and limitation of excessive physical exertion including straining. Palmer has demonstrated the adverse effect of the Valsalva maneuver in elevating esophageal variceal pressure.[220,224] Hoffbauer, Bollman and Grindlay found that eating produced prolonged and sustained elevation of pressure in the portal vein in experimental animals[144] That overeating may induce hemorrhagic esophageal varices in cirrhosis must be considered, and, perhaps, six daily meals instead

TABLE IV

HISTORICAL SUMMARY OF SHUNT PROCEDURES IN CIRRHOSIS

Eck	1877	Experimental Eck fistula
Tansini (Whipple)	1902	Eck fistual, portal vein implanted into vena cava, successful, lived 4 months
Vidal	1903	
Demartal	1910	Side-to-side anastomosis of vena cava and portal vein, died of anuria
Villard and Tavernier	1910	Anastomosis of ovarian vein to superior vena cava
Gunn	1911	Anastomosis of right ovarian vein and portal vein
Lenoir	1912	Eck fistula
Rosenstein	1911	Eck fistula for ascites
Meursing	1912	Anastomosis of spermatic vein to splenic vein
Borgoras	1913	Transplantation of superior mesenteric vein into the inferior vena cava
Whipple, Blakemore, and Lord	1945	Nonsuture anastomosis of portal vein to inferior vena cava and splenic to renal veins
Blalock, Blakemore	1946 1947	Anastomosis of splenic and renal veins, end to side

with cirrhosis and bleeding esophageal varices for a shunt procedure, the evaluation of various physical and laboratory criteria is necessary in order to minimize the surgical risk. It is generally conceded that the patient should be in the optimum physical condition and that further complications of cirrhosis such as ascites, anemia, hepatic insufficiency and infection be adequately treated. Ascites, however, has not constituted a contraindication for shunt operations in some clinics. Intractable ascites has been reported to be treated effectively by the establishment of portacaval shunt [13,37,38,112,135,148,150]

Patients with cirrhosis generally tolerate surgery unusually well if hepatocellular function is not too impaired and general anesthesia, cyclopropane in particular, or spinal anesthesia is employed [57,210,234,238,251] The determinations of various tests of hepatic function are beneficial in selecting cirrhotic patients for shunt procedures. These criteria are (1) serum albumin over 3 gm/100 cc, (2) bromsulfalein retention under 15 per cent in 45 minutes, (3) prothrombin time of 60 per cent or greater, (4) cephalin-cholesterol flocculation of 2+ or less. Marked jaundice or a total serum bilirubin over 5 mg/100 cc of blood are usually considered a definite contraindication for elective major surgery in patients with cirrhosis. In addition to these tests, it may be advisable to determine the serial values of the serum cholinesterase or serum transaminase,

TABLE III
RESULTS OF
EMERGENCY AND DEFINITIVE SURGICAL PROCEDURES IN CIRRHOSIS OF THE LIVER

Type	*No Cases*	*Reason*	*Range of Survival Years*	*No Dead*	*Cause of Death*
		Portal Cirrhosis			
Portacaval shunt	9	Esophageal Hemorrhage	0 6	3	Esophagel Hemorrhage—4
Splenorenal shunt	2	Esophageal Hemorrhage	½ 3	2	Esophageal Hemorrhage—2
Ligation hepatic artery	4	Esophageal Hemorrhage	0 4	3	Hepatic Insufficiency—3
Splenectomy	7	Hypersplenism Esophageal Hemorrhage	0 3	5	Esophageal Hemorrhage—4 Hepatic Insufficiency—1
Ligation splenic artery Coronary vein, L Gastric artery	3	Esophageal Hemorrhage	0	2	Esophageal Hemorrhage—2
Sclerosis esophageal veins	5	Esophageal Hemorrhage	½ 3	3	Hepatic Insufficiency—2 Esophageal Hemorrhage—1
Crosby Cooney button	3	Ascites	1 4	1	Hepatic Insufficiency
		Postnecrotic Cirrhosis			
Portacaval shunt	6	Esophageal Hemorrhage	0 3½	4	Hepatic Insufficiency—1 Esophageal Hemorrhage—3
Splenorenal shunt	2	Esophageal Hemorrhage	0-1½	1	Esophageal Hemorrhage
Ligation hepatic artery	2	Esophageal Hemorrhage	0	1	Hepatic Insufficiency
Splenectomy	3	Hypersplenism Esophageal Hemorrhage	1	2	Esophageal Hemorrhage
Esophagogastrectomy (Sleeve resection)	1	Esophageal Hemorrhage	1¾	0	0
		Progressive Hepatolenticular Degeneration			
Splenectomy	1	Hypersplenism	1	1	Hepatic Insufficiency

*This series was accumulated from the combined medical and surgical services at the Ochsner Clinic and Charity Hospital at New Orleans La, and in private practice

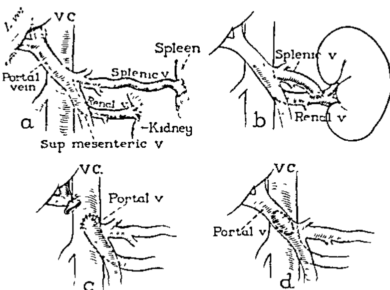


FIG 16a Normal anatomic distribution of inferior vena cava and portal vein and their immediate tributaries
FIG 16b Splenectomy and splenorenal shunt
FIG 16c End to-side direct portacaval shunt
FIG 16d Side to side direct portacaval shunt (Courtesy, Hallenbeck, G. A — S Clin North America—August, 1955)

which indicate the degree of hepatocellular dysfunction Often abnormal results of the standard hepatic function tests, namely, the cephalin-cholesterol flocculation, the thymol turbidity and flocculation, and the zinc sulfate turbidity, are unreliable in selection of patients because their values may never return to acceptable levels by the time a shunt procedure becomes necessary The selection of cirrhotic patients for shunt surgery is individual rather than general, however, shunt procedures should never be considered until maximal hepatocellular function is regained, because the operative and postoperative mortalities of poorly or hastily prepared patients are high

The most effective shunt operation for patients with cirrhosis and esophageal varices has been the portacaval shunt This is super-

TABLE V
TREATMENT OF INTRAHEPATIC BLOCK FOR PORTAL HYPERTENSION
(DATA FROM A REVIEW OF THE LITERATURE)

Operation	Total Number of Patients	Operative Mortality		Cause of Death: Hemorrhage		Cause of Death: Hepatic Failure		Recurrent Hemorrhage	
		Number of Patients	Per cent of Total	Number of Patients	Per cent of Total	Number of Patients	Per cent of Total	Number of Patients	Per cent of Total
Portacaval shunt	556	76	13	23	5	5	1	20	4
Splenectomy	136	52	38	9	10	16	19	33	48
Splenorenal shunt	107	18	16	9	10	20	22	33	37
Hepatic artery ligation	40	7	18	0	—	8	21	9	23
Suture	28	8	28	0	—	11	39	9	32
Esophagogastric resection	11	4	36	1	14	1	14	1	14
Splenic artery ligation	8	0	—	1	12	0	—	1	12
Devascularization	7	3	43	—	0	0	—	1	25
Mediastinal packing	6	0	—	33	0	0	—	3	50
Makeshift	4	0	—	25	0	0	—	3	75
Vagotomy	2	0	—	—	0	0	—	1	50

Britton, R C—Cleveland Clinic Quarterly—April 1958

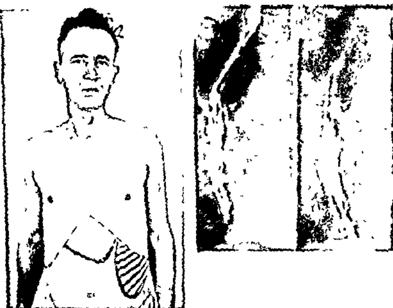


Fig. 17a. A patient with portal cirrhosis and moderate hypersplenism, etiology unknown. Physical findings were absent except hepatosplenomegaly. Clinical onset was massive hemorrhagic esophageal varices; a complete hematological investigation revealed, in particular, leukopenia, thrombocytopenia and a normocytic normochromic anemia; a hepatic battery of tests revealed normal results except for the bromosulfalein retention which was 9 per cent in forty-five minutes. Histologically, needle biopsy of the liver confirmed portal cirrhosis.

Fig. 17b. Roentgenograms of the esophagus of same patient disclosing enlarged esophageal varices in the greater length of the esophagus.

cirrhosis upon whom a portacaval shunt is to be performed and improved surgical technique and experience of surgeons (Table I). For example, Blakemore noted that the postoperative mortality in his initial series of 117 patients was 23 per cent, and in a later series of 85 patients, 15 per cent.[21,39] Child reports that the postoperative mortality of portacaval and splenorenal shunts in a collected series of 362 cases was 14 per cent.[59,59] An apparent objection to the portacaval shunt has been raised in that hepatic insufficiency occurred twice as often following portacaval than splenorenal

ior to a splenorenal shunt because of the larger size of the veins involved and is a more direct shunt because blood traversing the anastomosis runs only a few centimeters from the main tributary, the superior mesenteric vein, to the inferior caval system rather than coursing through the longer splenic vein which often is irregular or tortuous. Also, due to physiological fluctuations in portal hypertension in patients with cirrhosis which may depend upon their cooperation in abstaining from alcohol and adhering to a strict medical regimen, a splenorenal shunt is more apt to occlude by thrombosis or atrophy. The portacaval shunt, on the other hand, has a better chance of retaining its original size. Hunt has reported that the average speed of blood flow in the portal vein in patients with cirrhosis was increased from 5 to 12 cm./second following a portacaval shunt and from 5 to 7 cm./second following a splenorenal shunt.[148] Frequently, the choice of a shunt procedure depends upon other factors, such as the ability and skill of the surgeon, the presence of an enlarged spleen, hypersplenism, a cavernous or thrombosed portal vein and adhesions from previous abdominal operations, in which case splenectomy and a splenorenal shunt are paramount (Fig. 17). The diagnostic use of splenoportography often is an influential test in deciding the type of shunt procedure technically feasible.

After Whipple and Blakemore and Lord reported that portacaval shunts would ameliorate portal hypertension in patients with cirrhosis, impressive therapeutic results were acclaimed from other clinics.[31,39,59,136,152,157,158,161,162,181,185,186,188,189,231,232,264,265,312,316,318] Blakemore and Lord initially employed vitallium tubes to establish portacaval shunts.[40] Currently, an end-to-side total anastomosis is recommended. The distal end of the portal vein is ligated and anastomosed to the side of the inferior vena cava. A side-to-side partial portacaval shunt performed without interrupting the continuity of the portal vein is not generally employed at present. In this situation, the liver is deprived of much of its badly needed arterial and venous blood, because the hepatic arterial blood flow then would be shunted through the anastomosis, further impairing hepatocellular function.

Progressively better surgical results of portacaval shunts in the past decade indicate a better preoperative selection of patients with

tency of a portacaval shunt. These are splenoportography, percutaneous transhepatic or transsplenic determination of venous pressure, hepatic venous catheterization, catheterization and visualization of the vena cava, ammonium citrate tolerance test, intraduodenal instillation of bile salts, or a radioactive sodium test.[3,62,103,127] In general, the recurrence rate of further esophageal hemorrhage following properly executed shunt procedures is extraordinarily low, even though many variables enter into these statistics (Fig. 18). Child has described 56 cirrhotics with bleeding esophageal varices in whom portal decompression, mostly portacaval shunts were performed without recurrent esophageal bleeding.[28,59] Blakemore described 78 similar cases, of which 7 have bled since surgery.[27,35] Linton reported the following results: 60 (80 per cent) splenorenal shunts in which there were 3 cases (5 per cent) with slight bleeding not requiring hospitalization, 5 (8 per cent) with major bleeding, and 1 death (1.7 per cent); 18 portacaval shunts (20 per cent) with no eventual minor bleeding, 2 cases of major bleeding (11 per cent), and no deaths from bleeding.[179-182]



Fig. 17e. Gross surgical specimen from spleen of same case weighing 910 gm. Patient had a good result from a splenectomy and splenorenal shunt, immediate hematologic recovery following splenectomy.

shunts Ebeling and Linton and their co-workers state that there were 9 cases of hepatic insufficiency, fatal in 3 instances, in 24 portacaval shunts performed upon patients with moderate cirrhosis.[97] A splenorenal shunt was performed in 58 cases and was followed by hepatic insufficiency in 7 cases, fatal in 2, and by "hemorrhagic death" in 2 instances.

Sufficient material has been accumulated since 1945 to afford pertinent information on the eventual results of portacaval shunts performed in patients with cirrhosis and esophageal varices Invariably, there is an immediate reduction in the pressure in the portal vein following an end-to-side portacaval shunt, amounting to 10 to 15 cm of saline solution [59,151] In the event adequate portal decompression has not occurred, further esophageal hemorrhage is imminent Various tests may be employed to determine the pa-



Fig 17c. Roentgenogram of the stomach of same patient showing prominent gastric varices confined to the cardia and fundus of the stomach

Fig 17d Roentgenogram of the esophagus of the same patient several months following a successful splenorenal shunt Esophageal and gastric varices were absent roentgenologically.

tency of a portacaval shunt. These are splenoportography percutaneous transhepatic or transsplenic determination of venous pressure, hepatic venous catheterization, catheterization and visualization of the vena cava, ammonium citrate tolerance test, intraduodenal instillation of bile salts, or a radioactive sodium test.[3, 12, 103, 127] In general, the recurrence rate of further esophageal hemorrhage following properly executed shunt procedures is extraordinarily low, even though many variables enter into these statistics (Fig 18). Child has described 56 cirrhotics with bleeding esophageal varices in whom portal decompression, mostly portacaval shunts were performed without recurrent esophageal bleeding.[38, 39] Blakemore described 78 similar cases, of which 7 have bled since surgery.[37, 39] Linton reported the following results: 60 (80 per cent) splenorenal shunts in which there were 3 cases (5 per cent) with slight bleeding not requiring hospitalization, 5 (8 per cent) with major bleeding, and 1 death (1.7 per cent), 18 portacaval shunts (20 per cent) with no eventual minor bleeding, 2 cases of major bleeding (11 per cent), and no deaths from bleeding.[179, 182]



Fig 17e Gross surgical specimen from spleen of same case weighing 940 gm Patient had a good result from a splenectomy and splenorenal shunt immediate hematologic recovery following splenectomy

The effect of these shunts upon hepatic functions has interested several groups [36 38 58,59 107,108,178 181 188 221,225,231,232 312] In general, tests of hepatic function may not improve immediately following a shunt. Actually a side-to end portacaval shunt may produce tem-

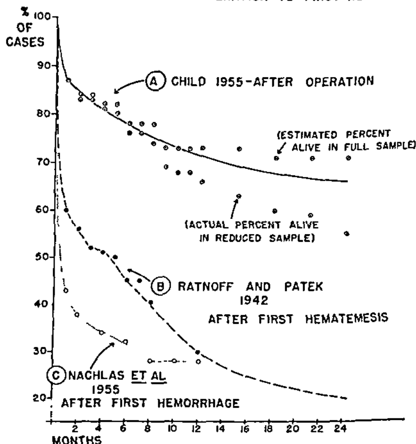


Fig. 18A. Survival curve of series at the New York and New England hospitals of 56 patients with cirrhosis subjected to portal decompression for variceal hemorrhage

Fig 18B (1942) Twelve month survival curve (redrawn) after first hematemesis according to Ratnoff and Patek.

Fig. 18C Twelve month survival curve after first hematemesis according to Nachlas *et al.* (1955) (Courtesy, Child, C. G, III—New England J. Med—1955)

porary and increased abnormal values in the hepatic function tests On the other hand, a ten year follow-up by Ellis, Linton, and Jones on 88 cirrhotics with splenorenal shunts (23 8 per cent mortality) and 37 cirrhotics with a direct portacaval shunt (10 5 per cent mortality) demonstrated increased survival rate, reduction in bleeding esophageal varices, and improvement in hepatic function [107,108] Macpherson and co-workers did not notice any deterioration in hepatic function following shunt operations, and suggest that the preoperative functional capacity of the liver rather than the adverse effects of operation per se is more significant prognostically.[189] It has been suggested that surgical portal decompression offers marked protective effect against initial and repeated esophageal hemorrhage, and, eventually, results in a high productive capacity of the patients [231] Episodic stupor and elevation of the blood ammonia following portacaval shunt has been described by Fisher and Faloon [115] Bradley and his co-workers have demonstrated that patients with cirrhosis have decreased hepatic blood flow after portacaval shunts, attributed to diversion of the portal blood from the liver to the systemic circulation [49] On the other hand, hepatic regeneration has been reported to depend on arterial blood flow more than portal blood flow [117,120,130,132,198,241] A splenorenal shunt has a less adverse effect on hepatic function tests, particularly the serum albumin, hepatic flocculation tests and serum bilirubin, than a portacaval shunt

A splenorenal shunt is the procedure of choice in patients with esophageal varices due to extrahepatic portal block, cirrhosis with marked splenomegaly or hypersplenism, or thrombosis or cavernous formation of the portal or splenic vein The outstanding proponents of splenorenal shunt in the treatment of patients with cirrhosis and bleeding esophageal varices have been Rousselot and Linton, respectively, and their co-workers.[108,177-182,264,265] While perhaps not as mechanically efficient in decompressing portal hypertension as the direct portacaval shunt, splenorenal shunt in their hands has been effective and associated with less postoperative hepatic failure and abnormality in liver function [97] Welch and Ramos report that bleeding recurred in 5 per cent of patients with portacaval shunts and 40 per cent with splenorenal shunts.[312] Their over-

all survival rate was 58 per cent and the operative mortality rate 15 per cent among 40 patients.

Various other portal to systemic venous shunts which may be technically feasible can be employed for venous decompression. Clatworthy has advocated a side-to-side anastomosis between the superior mesenteric vein and a divided proximal inferior vena cava whenever the portal or splenic veins are inaccessible for decompressive procedures.[52] The problem of the post-splenectomy bleeder has been considered in many reports, and shunts other than direct portacaval or splenorenal types must be considered in light of this complication [37-39 43 136,137]

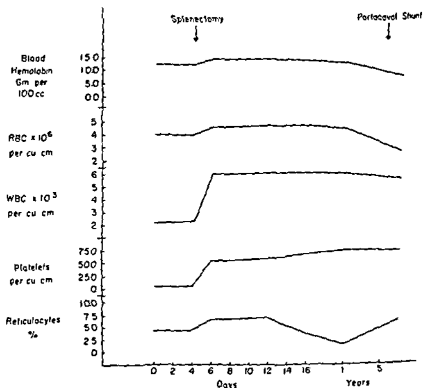


FIG. 19.

Ligation of the hepatic and splenic arteries has been recommended as a surgical treatment of portal hypertension in patients with cirrhosis and bleeding esophageal varices, particularly by Rienhoff in 1951 and, subsequently, by Berman [27 29 235] In general, the operation has been considered useless and the mortality prohibitive.[5 7,190 191 200 252] Its theoretical implications have already been alluded to

Finally, splenectomy is indicated usually for patients with cirrhosis with severe hypersplenism or in preparation for performing a splenorenal shunt [74,75 84 102 115 140 197 293] Secondary hypersplenism in cirrhosis is suddenly and dramatically corrected by splenectomy. This procedure is impractical for decreasing portal hypertension The mortality rate is about 10 per cent in the hands of a competent surgeon.[64 95 106 125 207 240 250] Jordan and Heck analyzed 98 cases of hypersplenism of all types observed at the Mayo Clinic.[134] The survival rate and the beneficial results in patients were no different in those with or without splenectomy. All too frequently, correction of leukopenia or thrombocytopenia is accomplished solely by splenectomy in patients with cirrhosis and hypersplenism only to have an abdominal abscess or hemorrhage, thrombosis of the portal vein, or hepatic insufficiency lead to demise. Recurrence of bleeding esophageal varices occurs in about 50 per cent of cases in which splenectomy has been performed for this purpose.[207,240]

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Chapter 15

ASCITES

INTRODUCTION

Ascites is an unique physical finding associated with certain specific diseases involving the liver, heart, kidney, peritoneum, thyroid gland, gonads and vascular or lymphatic systems Cirrhosis is one of the most prevalent world-wide diseases of which ascites is a main complication The term, ascites, was derived from the Greek word askos, meaning bag and was introduced in 1398 by Trenisa The Egyptians about 3000 B.C and Diocles of Carystos and Erasistratos in 350 B C., respectively, associated ascites with a diseased liver.[134,143,182] Ascites has had important historical implications and its relationship to cirrhosis and treatment by abdominal paracentesis and other measures has been recorded in ancient documents (Chapter 1)

In order to better understand the mechanism of ascites in cirrhosis in humans, certain information might be gathered from the results of experimental methods of producing ascites As early as 1728, experimental ascites was produced by Lower who ligated the supradiaphragmatic inferior vena cava [147] Since then, constriction or ligation of the thoracic inferior vena cava in the monkey, cat, dog and rat has been demonstrated to produce hepatic congestion and ascites.[31-34,115,116 118 119 127 156-158,164,166,265-267] Portal hypertension has also been demonstrated to play a secondary role in the pathogenesis of experimental ascites Hoffbauer, Bollman and Grindlay were unable to produce ascites by constricting the portal vein progressively with a cellophane band [116] Studies by other groups have demonstrated that ascites develops inconsistently by producing portal hypertension in experimental animals [27,32-34,72,80,81,132,141,199] A study by Volwiler, Grindlay and Bollman shows clearly that portal hypertension is not an essential factor in the pathogenesis of ascites [238] Two types of experimental ascites were produced in dogs, one by constricting the thoracic inferior vena cava, and the other by constricting the abdominal vena cava and portal vein and removal of

part of the circulating plasma protein, external plasmapheresis, thereby rendering the subjects hypoproteinemic The former method resulted in marked congestion of the liver, enlarged hilar lymphatics, increased hepatic lymph flow and ascites, the fluid of which contained increased protein. The latter technique, on the other hand, produced less ascites, containing a decreased amount of protein The primary importance of hepatic engorgement and transudation of hepatic lymph into the peritoneal cavity together with only the contributing role of portal hypertension in formation of ascites were the ultimate experimental conclusions. *Schilling* and McKee also produced experimental ascites by constriction of the thoracic vena cava and demonstrated decreased excretion of urinary sodium [161 166,219] Hyatt, Lawrence and Smith were able to produce massive ascites in dogs by this method when supplemented by the administration of salt.[115] They observed that the content of protein in the voluminous transudation from the capsule of the congested liver was similar to plasma and hepatic lymph

MECHANISM OF ASCITES IN HUMANS

One pathogenetic factor which is considered to regulate ascites in patients with cirrhosis is the plasma proteins Grenet in 1907 considered a relationship between plasma proteins and ascites in cirrhosis [42] Starling's law constitutes an important physiological principle governing the transfer of fluid from the blood stream to extravascular space This states that the colloidal osmotic force of the blood together with the hydrostatic pressure of tissue retain fluid intravascularly, whereas the colloidal osmotic force of the tissue fluid and the capillary hydrostatic pressure tend to move fluid interstitially [235 239] Capillaries are generally impermeable to the plasma protein, and the transudate that escapes is conveyed by the lymphatic system to the vascular system. In portal hypertension, however, the capillary hydrostatic pressure is conceivably increased This results in the loss of fluid into the tissue space which exceeds the physiological factors of return of fluid via the lymphatics and the colloidal osmotic force of the tissue fluid Loss of plasma proteins in the tissue space, internal plasmapheresis, further increases the osmotic force of tissue fluid. It has been demonstrated that ascitic fluid in cirrhosis exudes through the hepatic capsule into the

peritoneal cavity and that this fluid is derived from hepatic lymph [11,29,40,107,118,119] The animal experiments of Nix and Volwiler, respectively, further support this contention.[183,259] Hyatt and co-workers studied dogs with ascites and found persistent formation of drops of fluid on the surface of the liver.[118] This "liver-fluid" was collected, and the composition was found similar to hepatic lymph Baggenstoss and Cain demonstrated that the lymphatics draining the liver in the hepatoduodenal ligament are numerically increased, dilated, and thickened in patients with cirrhosis [11] Venous stasis, intrahepatic portal hypertension and necrosis were considered to be responsible pathogenic factors

In 1922 Filinski found that reversed albumin-globulin of the serum occurred in cirrhosis among other hepatic diseases.[88] The liver is considered to be the exclusive site for the synthesis and storage of albumin and fibrinogin and to a lesser extent of globulin [3,41,74,156,199 200 254,265,266] Miller and his co-workers studied the synthesis of protein in the perfused rat liver employing C^{14}-labelled lysine, and found that the liver synthesized albumin completely and about 80 per cent of globulin [171] In the diseased liver, extrahepatic tissues were capable of synthesizing some globulin from amino acids absorbed into the portal system This experiment offers a clue to explain hypoalbuminemia and hyperglobulinemia observed in patients with cirrhosis. Serum albumin, because of its smaller molecular size and increased concentration rather than serum globulin maintains the principle colloidal osmotic pressure of the blood [108] When the synthesis and storage of albumin is interrupted in cirrhosis, the osmotic pressure of the blood diminishes and ascites occurs, the degree of which is frequently correlated with the amount of hypoalbuminemia [8 25,51,113,126,178,194 195 200] However, that no correlation between ascites and hypoalbuminemia exists in cirrhosis has been contended by others [37,113,195,206] A frequent clinical observation in patients with cirrhosis is the onset or recurrence of ascites when the amount of serum albumin is decreased by an esophageal hemorrhage, alcoholism, thrombosis of the portal vein, or even infection The quantity of protein present in ascitic fluid in cirrhotics is invariably greater than in ascitic fluid in patients with congestive heart failure The diffusion of plasma protein into ascitic fluid and

establishment of an equilibrium between the respective osmotic pressures of the blood and ascitic fluid has been considered an important physiological feature in ascites.[1-8, 220] A significant clinical observation in patients with cirrhosis has been that the administration of salt poor serum albumin perpetuates the amount of protein in ascitic fluid and a further increase in the amount of ascites. An interchange of protein and water from plasma to ascites has been demonstrated by studies with radioactive C^{14}-plasma protein and tritium-labeled water.[204] In addition, a decreased circulating blood volume has been found in patients with cirrhosis using radioactive chromium tagged erythrocytes.[78] This feature is considered secondary to hypoalbuminemia. It appears that hypoalbuminemia plays a contributary role in the pathogenesis of ascites.

The role played by portal hypertension in the pathogenesis of ascites in patients was originally considered to be significant.[33, 79, 183, 264] However, the methods of producing experimental ascites alluded to earlier offer considerable evidence that portal hypertension does not produce ascites consistently of the type observed in patients with cirrhosis.[67, 113, 154] Clinically, ascites is not as predominant a finding in patients with thrombosis of the portal vein as it is in patients with thrombosis of the hepatic vein (Chiari's syndrome) or inferior vena cava. No correlation between portal hypertension and ascites was demonstrated in patients with cirrhosis by Rousselot and Thompson.[215] However, the investigation by Eisenmenger and Nickel mentions 5 patients with cirrhosis whose ascites disappeared after a portacaval shunt.[59] That portal hypertension generally produces ascites appears to be a remote feature with the exception of instances of very marked portal hypertension co-existing with severe hypoalbuminemia.

A more important factor concerned with the mechanism of ascites in patients with cirrhosis concerns renal function and electrolyte and water metabolism. Retention of sodium by the kidney and formation of ascites have been demonstrated to occur from operative occlusion of the thoracic vena cava. This is in contrast to obstruction of the abdominal vena cava or the portal vein in cirrhotics with ascites regardless of sodium intake.[69, 103, 104, 112, 139, 184-186, 219] It has been suggested that the mechanism of fluid and sodium retention

is identical in patients with cirrhosis and congestive heart failure.[89] The administration of sodium to patients with cirrhosis has been demonstrated to effect an increased rate of formation of ascites and edema.[47,48,80,87,131,136,137] On the other hand, dietary restriction of sodium produces an urinary excretion of sodium and water in patients with cirrhosis.[77-79,164-166] In cirrhosis as with congestive heart failure, "sodium saving" and reduction of glomerular filtration occurs during periods of ascites, and normal glomerular filtration develops with spontaneous reduction of ascites.[89,139,213] However, another study disclosed normal rates of glomerular filtration in patients with cirrhosis and ascites.[83] Therefore, some other abnormal renal mechanism may increase tubular absorption of sodium. Goodyer and his associates infused patients with cirrhosis with hypertonic saline, in whom most had normal glomerular filtration and renal plasma flow. They found diminished sodium excretion greater in cirrhosis with ascites than without ascites and postulated that sodium is retained by the kidneys as the result of increased tubular reabsorption.[105] Usually patients with cirrhosis and ascites excrete urinary sodium in the amount of 0.1 to 0.2 gm (5 to 10 mEq) per day. In addition, there is reduction in the amount of sodium in the sweat, saliva and feces and increased concentration of potassium in saliva and sweat.[19,79]

In a well-conducted investigation, Strub and his co-workers studied samples of the deltoid and gastrocnemius muscles obtained from 6 patients with cirrhosis accompanied by ascites and edema by various metabolic techniques or regulated sodium intake.[241,245] They found ascites and edema in cirrhosis represented essentially isotonic expansion of extracellular fluid in contrast to fluid retention of congestive heart failure, in which hypotonic expansion of both intracellular and extracellular water occurs. They also found that tissue overhydration in cirrhosis may persist and that extracellular fluid diminishes regardless of the type of diuretic therapy in the disappearance of overt ascites and edema (Figs 1, 2).

Impaired renal excretion of sodium in cirrhosis has been explained on a hormonal basis. In 1945 Ralli and her co-workers found that the urine of patients with cirrhosis and ascites when injected into hydrated rats delayed the excretion of urine in the rats

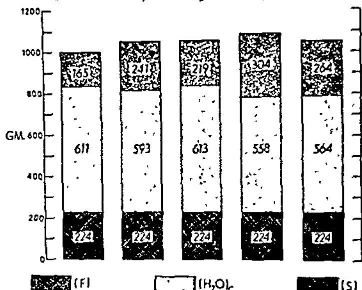


FIG 1 (Courtesy, Strub, Talso, and Kirsner—Gastroenterology—February, 1955)

[205, 206] The presence of increased amounts of an antidiuretic factor in patients with cirrhosis was postulated to explain ascites Increased amounts of an antidiuretic substance have been found in the blood and urine of patients with cirrhosis and ascites and in the

CHANGES IN BODY COMPARTMENTS DURING THERAPY OF CIRRHOSIS OF THE LIVER

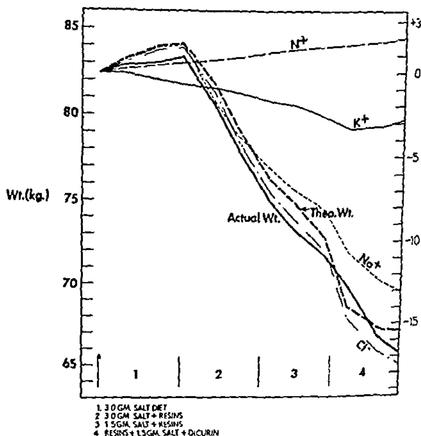


Fig. 2 (Courtesy, Strub, Talso, and Kirsner—Gastroenterology—February, 1955)

urine of patients with congestive heart failure.[15,109 142 242 257] However, these investigations have not been confirmed.[23 192 233,240 256 258,263,269] Thus it appears that the significance of an antidiuretic hormone in cirrhosis is doubtful as a cause of ascites It has also been noted that, in patients with cirrhosis or congestive heart disease, pitressin is normally inactivated.[268 269] Hypothalamic osmoreceptors respond to increased osmolarity by stimulating thirst and secretion

of antidiuretic hormone, causing renal tubular retention of water.[251]

The homeostasis of electrolytes and water is also regulated by the adrenal gland or adrenal stimulation from hypothalamic volumoreceptors. Adrenal hyperplasia or tumors and hormonal stimulation of this gland may provoke, among other features, ascites and edema. Increased production of desoxycorticosterone and corticoids have been implicated in cirrhosis and ascites.[41,125] Davis and his co-workers have emphasized the importance of desoxycorticosterone-like hormones in experimental production of ascites.[65,70] Increasing the vena cava pressure in adrenalectomized dogs led to ascites and retention of sodium only if large doses of desoxycorticosterone rather than cortisone were administered. It has also been demonstrated that the adrenocorticotropic hormone is capable of intensifying sodium and fluid retention in cirrhosis by augmenting the activity of corticoids on water and salt metabolism.[25,35,40] That the adrenal cortical hormones induce loss of intracellular potassium and an increase in intracellular sodium in cirrhosis has been concluded from another study.[110] These investigations implicate adrenal hormones in ascites by the retention of sodium and water in patients with cirrhosis. Effective sodium diuresis has been demonstrated in patients with cirrhosis and ascites by the administration of an inhibitor of adrenal steroid productor, amphenone or 3, 3-bis (p-aminophenyl) - 2 - butanone dihydrochloride. Unfortunately, its therapeutic usefulness is limited because of its sedative properties.[273]

In 1955 Conn described a new clinical syndrome, primary aldosteronism, in which the 18-aldehyde of corticosterone, aldosterone, is found in excessive amounts in the body.[35-50] This hormone is secreted by the adrenal cortex and causes retention of sodium.[151] Primary aldosteronism is a condition resulting from an aldosterone-secreting adrenal adenoma and is characterized by muscular weakness, intermittent tetany, polyuria, polydipsia, hypertension and a hypokalemic, hypernatremic alkalosis. The ascites occurring in cirrhosis has been postulated to be the consequence of secondary aldosteronism and normal production of hydrocortisone. However, this concept requires further clarification.[47,49,83,101,214]

Physiological retention of sodium and water by estrogens has

been demonstrated in animals.[190,231] Decreased inactivation of estrogens also has been considered to occur when the liver is diseased resulting in retention of water and sodium. Masculinization, testicular atrophy, alopecia, spider angioma, gynecomastia and possibly palmar erythema are the possible pathological manifestations of excessive amounts of estrogen in patients with hepatic disease.[13,17,129,142,175,215] Increased urinary estrogen has also been found in acute and chronic hepatic diseases.[73,101,196,217] Preedy and Aitkin found sustained retention of sodium chloride and water in 8 of 9 cases of cirrhosis with ascites following the administration of estradiol benzoate.[202,203] In cases of cirrhosis without ascites, the sodium and water retention following exogenously administered estradiol was only slightly greater than normal in 11 of 12 cirrhotics. They considered that decreased hepatic inactivation of estrogen was related more to disturbed hepatic circulation than to hepatocellular dysfunction in cirrhosis.

Another factor implicated in the pathogenesis of ascites and edema in cirrhosis has been the vasodepressor factor (VDM), elaborated by the liver, spleen, and striated muscles.[230-232] This substance acts by decreasing the vascular tone of the arterioles and increasing capillary hydrostatic pressure producing congestion. It is in equilibrium with a vasoexcitor factor (VEM) secreted by the kidneys. Hypotension, ascites, and edema occurring in patients with cirrhosis have been considered to be the result of VDM. In animals this substance has also been demonstrated to have an antidiuretic function. Cirrhotic patients with ascites have been shown to have VDM in the blood and ascites. A low prothrombin level in the ascitic fluid of patients with cirrhosis has been reported to distinguish ascites of malignant origin.[52]

The formation of ascites in cirrhosis may also be influenced slightly by increased intraperitoneal pressure and subsequent elevation of venous pressure within the inferior vena cava and also the hydrostatic effect of ascites.[122,159] Davidson has shown that ascites causes elevation of pressure in the inferior vena cava and may be contributory to the formation of fluid retention in cirrhosis.[67] Repeated abdominal paracentesis are frequently followed by an increased rate in the production of ascites and disturbance in water

and electrolyte balance. Many, therefore, feel that withholding a paracentesis as long as possible is advantageous despite stretching the abdominal wall. The intraperitoneal pressure, nevertheless, apparently only slightly influences the formation of ascites.[83]

Of the several mechanisms postulated to account for the pathogenesis of ascites in patients with cirrhosis, it would also appear that fibrosis and, in particular, nodular regeneration in the cirrhotic liver are sufficient to distort intrahepatic circulation and constrict the hepatic venules, thus producing increased venous pressure in the hepatic vein and portal vein. As a result, hepatic lymph rich in protein exudes into the peritoneal cavity. Impaired synthesis of albumin in cirrhosis causes decreased plasma osmotic pressure. The osmotic force of ascitic fluid is increased by hepatic lymph. Transudation of the fluid from the blood into the peritoneal cavity results with loss of sodium, and a seemingly continuous cycle of loss of protein, sodium and lymph into the peritoneal cavity may occur in cirrhosis. Studies have also disclosed that there is a constant circulation of fluid and albumin between the blood and peritoneal cavity in the cirrhotic with ascites.[141-166,204,220] Hypoproteinemia has also been considered by Kark to augment ascites in cirrhosis by directly influencing capillary permeability through the depletion of the content of protein of the endothelium.[124,125]

In conclusion, it appears that ascites and edema occurring in patients with cirrhosis are due to multiple factors rather than a singular factor (Table I). Increased pressure in the hepatic venules together with impaired hepatic function may be the important initiating pathogenetic factors. As a result, failure of the liver to inactivate estrogen and adrenal hormones, hypoalbuminemia, transudation of hepatic lymph and decreased tubular reabsorption of sodium, in particular, further potentiate ascites and edema and augment a vicious cycle of depletion of constituents of the blood and repletion of those of ascites and edema.

COMPLICATIONS OF ASCITES

The complications of ascites in patients with cirrhosis are represented by certain physical findings or abnormalities in the fluid and electrolyte metabolism. Umbilical, inguinal and ventral hern-

TABLE I
MULTIPLE PATHOGENIC FACTORS IN ASCITES AND EDEMA OF CIRRHOSIS

Hepatocellular Necrosis	*Hepatic Lymphangiectasis and Lymphedema*
1 Hypoalbuminemia	1 Intraperitoneal Pressure
2 Incomplete Inactivation of Adrenal and Gonadal Hormones	2 Ascites
3 Increased Capillary Permeability	3 Increased Osmotic Pressure of Ascitic Fluid
4 Vasodepressor Factor	
5 Malabsorption Syndrome	
6 Anorexia	
Impaired Renal Hemodynamics	*Nodular Regeneration, Fibrosis and Portavenous and Arteriovenous Anastomosis of Liver*
1 Reduction in Renal Plasma Flow	1 Intrahepatic Portal Hypertension
2 Reduction in Glomerular Filtration Rate	2 Increased Venous Pressure of Vena Cava
3 Increased Tubular Reabsorption of Sodium	3 Increased Capillary and Venule Hydrostatic Pressure
	4 Volume Receptor Stimulators (Osmoreceptors)?
	5 Gastrointestinal Hemorrhage

ias occur in this condition That the high incidence of hernia in patients with cirrhosis is due to an inborn defect of the connective tissue rather than ascites has been contended by Tanyol and his associates [240-243] They found that not only was the incidence of hernia high in cirrhosis, but, in most instances, it occurred several years prior to or in the complete absence of ascites Abdominal distention due to ascites may impair respiration resulting in reductions of the vital capacity, maximum breathing capacity, breathing reserve, and arterial oxygen saturation, and cyanosis.[2] Consequently, the effectiveness of cough is impaired, augmenting pulmonary atelectasis and bronchopneumonia Pleural or pericardial effusion are frequently associated with ascites Elevation of the diaphragm due to ascites may increase right auricular and intrapleural pressures [227] Ascites, which may be associated with gastrointestinal congestion or edema, may impair the appetite, alter bowel habit and induce a malabsorption syndrome.

The abnormal electrolyte and water metabolism occurring as the direct result of ascites or from the treatment of ascites constitute

a more significant risk to the patient.[8,222] It is known that the compensatory capacity of fluid and electrolyte regulatory mechanisms in older patients are reduced, indicating that replacement therapy must be anticipated or either prevented and quickly corrected with individualized management.[209] Hyponatremia or the salt-depletion syndrome may result from abdominal paracentesis, environmental heat, therapeutic diuresis, or consuming a diet low in salt. The clinical picture of hyponatremia is characterized by weakness, nausea, vomiting, apathy, abdominal and muscular cramps, impaired appetite, dehydration, arterial hypotension or vascular collapse, tachycardia, diminished pulse pressure, hemoconcentration, and oliguria, anuria or azotemia.[57,93,77,79,97,99,117,138,173,150,212,223,256] Mental confusion and drowsiness may be so extraordinary as to mimic impending hepatic coma. Renal insufficiency has been reported to be due to sodium depletion.[152,223] Sodium depletion in the extracellular compartment may produce decreased glomerular filtration.[43] Depletion of serum sodium therapeutically also induces hypotonic fluid in the extracellular compartment. If water is inadvertently administered to patients with hyponatremia, fluid entering the intracellular compartment increases, further depleting serum sodium and exacerbating these symptoms.[117,179] Mercurial diuretics are known to enhance not only the excretion of sodium but chloride.[172,209] The salt-deficiency syndrome may be corrected by the intravenous administration of 5 per cent sodium chloride in water preferably in amounts of 250 cc. at a time. Amelioration of symptoms promptly appears following this therapy. An increase in extracellular fluid and hyponatremia may perpetuate hepatic failure as the result of dietary sodium restriction. Occasionally, if hypertonic saline is administered to patients with terminal hepatic failure *who have already been treated by a sodium restricted regimen, the* extracellular fluid is further increased and hyponatremia persists. This unusual terminal finding has been referred to as "dilution hyponatremia," the treatment of which has not proved satisfactory.[77,79,228]

Hypernatremia occurs when the level of serum sodium exceeds 150 mEq./liter and is present under certain circumstances in a patient with cirrhosis and ascites. These are parenteral administration

of excessive sodium, renal insufficiency, adrenal corticoid therapy, dehydration, central nervous system injury, nasogastric tube feeding, diabetic coma and profuse intravenous saline, and in elderly patients, excessive heat, fever, or toxemias.[60,84,150,207,221,271] Dry skin, tachypnea, stupor, hyperthermia and muscular irritability are observed in patients with hypernatremia. The treatment of this condition is the oral or intravenous administration of nonsaline fluids. The administration of potassium chloride may ameliorate chronic sodium chloride toxicity.[133,164]

Another electrolytic complication that may be found in patients with cirrhosis and ascites is hypokaliemia or hypopotassemia (Fig. 3).[4,30,61-63,212] This may be the result of the administration and retention of water which produces dilution of the extracellular and intracellular fluids. It may be aggravated by associated conditions in which excretion of water is defective, such as, lower nephron nephrosis, adrenal insufficiency and congestive heart failure and as a result of the transfer of extracellular potassium into the cells by the administration of testosterone, intravenous glucose, overhydration following dehydration, or acidosis. Also it may result from excessive saline and water overload, vomiting, diarrhea, excessive gastrointestinal secretions, therapy with non-potassium cation-exchange resins, diuresis, adrenal corticoid therapy, malabsorption syndrome, malnutrition, use of sodium-restricted diets, de Toni-Fanconi syndrome or inadequate intake of potassium.[38,61-63,83,224] Hypokaliemia is invariably associated with a hypochloremic alkalosis and frequently with hyponatremia. The clinical manifestations of potassium depletion are weakness and hypotonicity of skeletal muscles progressing to paralysis, dyspnea, cyanosis, paralytic ileus, nausea and vomiting. Functional disturbances of the myocardium account for cardiac enlargement, widened pulse pressure and congestive heart failure.[61] Renal insufficiency, potassium-depletion nephropathy, has been described.[211] The electrocardiographic evidence of hypokaliemia is prolongation and depression of the Q-T interval, depression and inversion of the T wave, round, prolonged T wave, depression of the ST segment, inversion of the P waves, ventricular extrasystoles, and auriculoventricular block (Figs. 3, 4a). Hypokaliemia is frequently associated with hepatic

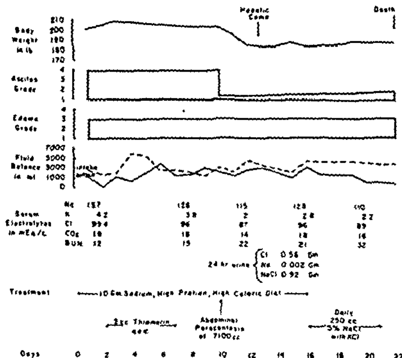


FIG 3 Hypokalemic hypochloremic acidosis terminal "dilutional" hyponatremia and renal insufficiency in a patient with portal cirrhosis, refractory ascites and edema hepatic coma developed following abdominal paracentesis

insufficiency.[8,52] This electrolyte disorder is treated by correction of the underlying disorder and replacement therapy with potassium An oral potassium salt, potassium triplex, of which 10 cc is equivalent to 30 mEq, may be prescribed orally

Hyperkaliemia or hyperpotassemia may be found in patients with hepatic failure, renal insufficiency, excessive potassium therapy, oliguria, shock, dehydration and diabetic acidosis (Figs. 4, 5) Automatic protection against hyperkaliemia is afforded by the cells,

which retain potassium.[103] Hyperkaliemia induces such electrocardiographic changes as prolonged conduction time, sharp, high T waves, increased duration of the P-R interval producing auricular standstill, cardiac arrhythmias and eventually heart block. The clinical features are acral numbness and paresthesias, mental confusion, listlessness, gray pallor, vascular collapse, flaccid paralysis, and cardiac arrest Treatment is directed at the basic underlying disorder, avoidance of administration potassium salts, correction of sodium and water depletion and the parenteral use of glucose.

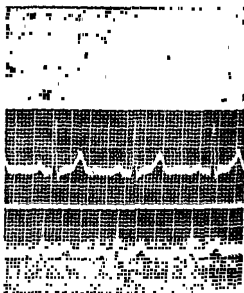


FIG 4a Three standard leads of an electrocardiogram obtained from a patient with portal cirrhosis and ascites Hyperkaliemia was present (Figure 5), producing the inevitable peaking of the T waves, usually marked narrowing of their bases, and, in severe instances, widening of the QRS complex and absent P waves

Other less significant electrolytic imbalances may occur in the management of ascites in cirrhosis Hypochloremia may accompany sodium or potassium deficits during the loss of gastrointestinal fluids, diuresis, or abdominal paracentesis Treatment is sodium or potassium chloride replacement. Ammonium chloride should not be employed in any replacement therapy in cirrhosis because

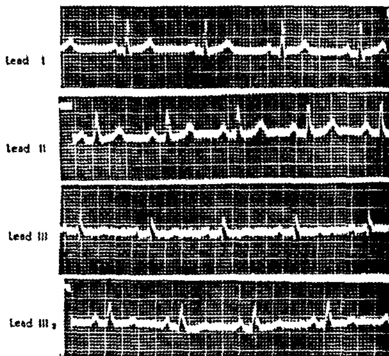


FIG 46 Normal electrocardiogram after treatment of hyperkalemia

of ammonium toxicity, and calcium chloride therapy is too hazardous particularly if associated with renal insufficiency [213] Alcoholism and cirrhosis have been observed to be associated with a magnesium deficiency syndrome, in which the clinical manifestations are muscular tremor convulsions, choreiform movements, delirium pain and paresthesias of the legs, and severe burning sensation of the feet Administration of non hypnotic doses of magnesium salts alleviates these symptoms Flink recommends 8 to 10 gm of magnesium sulfate intramuscularly in four or five divided doses the first day and 1 to 2 gm daily for three to five days thereafter [95]

Ascites and its management may be associated with disturbances in water balance [32 75 160 173] Dehydration resulting from fluid deprivation results in a hypertonic extracellular fluid and decreased

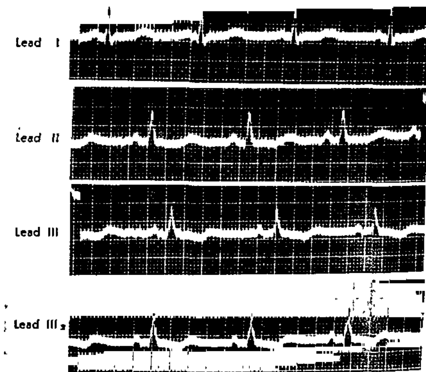


FIG 4c Electrocardiogram in a patient with hypokaliemia, sinus bradycardia, and prolonged Q T interval, and wide T waves

volume of extracellular fluid Thirst, fever, headache, dry skin, dry tongue, desiccation, restlessness, full pulse, normal blood pressure, and scanty concentrated urine are observed in this condition Treatment is water replacement Dehydration resulting from loss of electrolytes has already been alluded to, which, in turn, results in hypotonic extracellular fluid and decreased volume of extracellular fluid Weakness, pallor, hypotension, oliguria or anuria and absence of thirst are the cardinal symptoms However, *deprivation of* both water and electrolytes, "mixed dehydration," is more commonly seen. Overhydration, on the other hand, may result from excessive saline administration or cardiovascular-renal disease and is associated with increased volume of extracellular fluid and hypertonicity

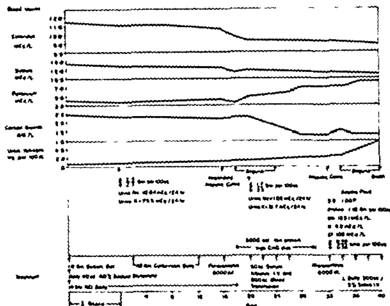


Fig 5 Development of hyponatremic, hyperkalemic acidosis renal insufficiency and hepatic coma in a patient with postnecrotic cirrhosis

of the extracellular fluid associated with edema Ingestion of excessive amounts of water, water intoxication, leads to increased volume and hypotonicity of the extracellular fluid This syndrome manifests itself by nervousness, salivation, and vomiting, and, when severe, disorientation, stupor, irregular twitching movements of the extremities and convulsions Treatment is the administration of a solution containing hypertonic saline

Disturbances in the acid-base balance also occur in cirrhosis Metabolic acidosis manifest by decreased pH and carbon dioxide combining power of the blood is also observed in patients with hepatic insufficiency Respiratory alkalosis in which the pH of the blood is increased and the carbon dioxide combining power is decreased possibly due to ammonia excess has been reported in patients with advanced cirrhosis [235]

TREATMENT OF ASCITES AND EDEMA

The management of ascites and edema in patients with cirrhosis is directed primarily toward improving hepatocellular function, decreasing the renal retention of sodium and improving hypoalbuminemia. This consists of abstinence from alcoholic beverages, optimal bedrest, a low-sodium, high-protein, high-caloric diet and possibly the therapeutic use of a pharmaceutical diuretic, salt-poor serum albumin, abdominal paracentesis or various surgical procedures. It is surprising that in due time an occasional patient with cirrhosis, ascites and edema will have a spontaneous diuresis particularly if adequate bedrest and the aforementioned diet are employed (Fig. 6). This observation has cautioned the experienced clinician against indiscriminate use of diuretics or hasty performance of an abdominal paracentesis, both of which procedures may also produce adverse complications.[1,29,30,136,180,231]

Adequate bedrest should be advocated for all patients with cirrhosis and ascites. While this recommendation should not be abused, usually complete bedrest with bathroom privileges employed initially, with a later regimen of eight to twelve hours of sleep, an afternoon nap of two hours, and restriction of activity are adequate. Slight elevation of the head of the bed offers more bodily comfort and less respiratory difficulty. Bedrest in the supine position is known to decrease significantly the venous pressure in the hepatic vein. Usually the cirrhotic with ascites is so debilitated and uncomfortable from abdominal tension that complete bedrest is readily accepted. In order to prevent certain complications resulting from bedrest such as peripheral thrombosis, weakness, stiff joints, muscular hypotonicity, mental depression, impaired appetite, protein catabolism, bronchopneumonia, urinary infection and osteoporosis, gradual resumption of ambulatory activity is recommended after at least one week of bedrest. Hospitalization for general supportive measures is advocated in most patients to properly regain dietary and hygienic habits and rest.

A low-sodium, high-protein, high-caloric diet has been found invaluable in the treatment of patients with cirrhosis and ascites.[210] Dietary sodium restriction amounting to 200 to 500 mg. of sodium equivalent to 0.5 to 1.2 gm. of sodium chloride daily have been

demonstrated to produce a satisfactory and often dramatic diuresis (Table II)[10, 65, 66, 74, 87, 98-99, 136, 157, 168, 178-180] The physician should check the sodium content of the local water supply before prescribing a sodium-restricted diet In many instances the content of sodium in the local public water supply is unsuitable for this diet and distilled water may be substituted[179] Once diuresis occurs, the volume of urine increases and the weight of the patient and amount of ascites diminishes. Davidson treated 30 patients with cirrhosis and ascites with sodium restricted diets (200 mg daily). *Prompt* diuresis occurred *in 4* patients, delayed diuresis (three *to sixteen* months) in 11 patients and failure from this therapy was [illegible] in 12 patients Kark [illegible]
level of sodium [illegible]
tein status" in [illegible] cirrhosis and ascites and advocates administration of a rigid diet containing 250 mg or less of sodium daily[125] Increments of sodium are added to the limits of tolerance depending upon gain of weight and reaccumulation of fluid On the other hand, in certain patients restriction of more than 500 mg of sodium per day may be required to assure adequate diuresis That one patient with cirrhosis and ascites may respond to a 3.0 gm sodium chloride diet and another to further limitations before adequate diuresis develops has been considered "individual reactivity" (Table III) (Fig 6)[211]

It is mandatory to obtain the weight of the patient daily preferably at the same time each morning and also to maintain a chart of this body weight Increased or sustained body weight may indicate inadequate dietary sodium restriction, unimproved hepatocellular function, abuse of ambulation, failure of diuretics, continued hepatotoxic agents, alcoholism or the low salt syndrome Unpalatability of the sodium-restricted diet may be reduced by prescribing and properly using certain sodium-free salt substitutes (Chapter 17) Once satisfactory diuresis is induced and hepatocellular function regained, the restriction of sodium may be modified Resolution of ascites and edema eventually leads to increased urinary excretion of sodium per day The hazards of sodium restriction have already been mentioned Imperative as dietary sodium restriction is in the treatment of ascites, a diet adequate in

TABLE II

CLINICAL AND LABORATORY DATA OF A 45 YEAR OLD MALE WITH PORTAL CIRRHOSIS ASCITES EDEMA AND IMPENDING HEPATIC COMA

Body Wgt lbs (170, 160, 140)

Ascites (Gr 1-4) (4, 2, 0)

Edema (Gr 1-4) (4, 2, 0)

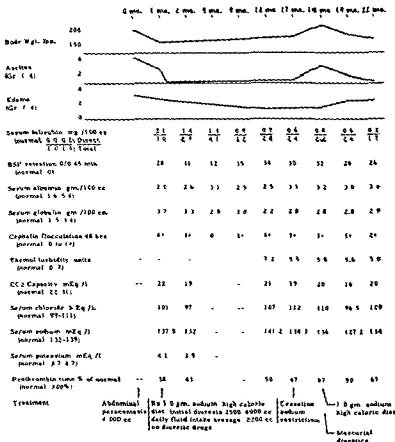
Days	1	7	13	19	25	31	37	43	49	52	12 mo.	14 mo.	20 mo.	24 mo.
Serum bilirubin mg./100 cc (normal 0.0-0.2) Direct / (1.0-1.5) Total	5.9/12.7	6.2/12.0	6.0/11.4	5.4/20.6	4.1/8.9		3.4/7.1	2.2/6.3		0.8/2.3	0.9/1.9	0.6/1.6	3.6/3.5	0.6/1.7
BSP retention 45 min (normal 6)								36		19	27	23	35	23
Serum albumin gm./100 cc (normal 3.6-5.4)	2.4	2.6	3.0	3.0	3.2		3.2	3.9		4.3	3.0	3.5	4.1	4.2
Serum globulin gm./100 cc (normal 1.5-3.4)	3.6	3.6	3.6	3.6	3.6		3.6	3.4		3.4	3.2	2.1	2.0	2.9
Cephalin flocculation 48 hr (normal 0 to 1+)	3+	3+	3+	3+	3+		3+	3+		3+	1	4	4	4
Thymol turbidity units (normal 0-7)	17.2	16.9	17.0	16.6	15.2		14.0	12		10	8.0	5.6	6.6	8.4
CO_2 capacity mEq/l (normal 22-31)	17	18	2	18	22		–	20		20			37.4	17.2
Serum chloride mEq/l (normal 99-111)	109	104	99	116.5	113.6		[illegible]	[illegible]		101.2			108.4	106.2
Serum sodium mEq/l (normal 132-139)	144	142	[illegible]	138	125		[illegible]	[illegible]		126.8			135.2	129.2
Serum potassium mEq/l (normal 3.7-4.3)	4.7	3.8	3.9	4.	4.2		4.1	3.9		4.2			4.5	4.4

Treatment: Moderate protein high carbohydrate high caloric 1.0 gm sodium chloride diet, ounce yeast, vitamin K, vitamins, initial bedrest and abstinence from alcohol.

ALCOHOLIC DEBAUCH (at 20 mo.)

TABLE III

CLINICAL COURSE AND LABORATORY DATA OF A 31 YEAR OLD MALE WITH ALCOHOLIC PORTAL CIRRHOSIS



	0 mo.	1 mo.	2 mo.	5 mo.	9 mo.	12 mo.	17 mo.	18 mo.	19 mo.	22 mo.
Serum bilirubin mg./100 cc (normal 0.0-0.2 Direct / 1.0-1.5 Total)		2.1/3.0	1.4/2.7	1.1/4.1	0.9/1.2	0.7/2.8	0.6/2.4	0.8/2.6	0.6/2.4	0.7/1.7
BSP retention 0/0 45 min. (normal 0)		28	31	12	35	34	30	32	28	26
Serum albumin gm./100 cc (normal 3.4-5.4)		2.0	2.6	3.1	2.5	2.5	3.1	3.2	3.0	3.4
Serum globulin gm./100 cc. (normal 1.5-3.4)		3.7	3.3	2.9	3.0	2.2	2.8	2.8	2.8	2.9
Cephalin flocculation 48 hrs. (normal 0 to 1+)		4+	1+	0	1+	1+	1+	3+	5+	2+
Thymol turbidity units (normal 0-7)	-	-	-			7.2	5.3	5.8	5.6	3.8
CO2 Capacity mEq./l. (normal 22-31)	--	22	19		-	23	19	20	16	20
Serum chloride mEq./l. (normal 99-111)		101	97	-	--	107	112	110	96.5	109
Serum sodium mEq./l. (normal 132-139)		137.5	132	-	-	141.2	138.3	136	127.2	134
Serum potassium mEq./l. (normal 3.7-4.7)		4.1	3.9	-						
Prothrombin time % of normal (normal 100%)	--	38	43		-	50	47	67	50	67

Treatment: Abdominal paracentesis 4,000 cc | Rx 1.0 gm. sodium high calorie diet, initial diuresis 2500-4000 cc daily fluid intake average 2200 cc, no diuretic drugs | Cessation sodium restriction | 1.0 gm. sodium high caloric diet | Mercurial diuretics

the amount of protein and calories is also necessary for restoration of hepatocellular necrosis. Many patients with advanced cirrhosis have a negative nitrogen balance which is ameliorated by adequate intake of protein.[89,90,124,125,126,167] Protein malnutrition has been considered to play an important role in the perpetuation of ascites

and edema (Fig 7) [65,119] Special low-sodium foods can be secured in most large grocery stores (Chapter 17). The clinician will find that a delicate dietary balance exists between the recommended and optimal amounts of protein, sodium and calories, and the requirement necessary for elimination of retention of fluid, restoration of hepatocellular activity, and malnutrition. In addition, diets low in sodium are expensive and often cannot be afforded by the patient, in particular, the alcoholic It is unnecessary to restrict die-

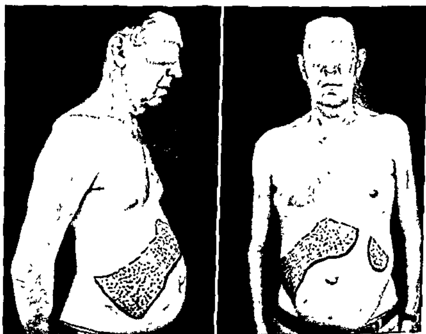


Fig 6a and b Sagittal and anterior views of a patient with malnutritional portal cirrhosis, ascites, hepatomegaly, splenomegaly (minimal hypersplenism), umbilical hernia, pectoral alopecia, gynecomastia, abdominal venous collateral circulation, and loss of weight Photographed prior to therapeutic management

Fig 6c and d Sagittal and anterior views of the same patient six months following conventional treatment of this condition especially ascites and impending hepatic coma An unusual therapeutic result, in which neither an abdominal paracentesis nor any diuretic agents were employed except a sodium restrict diet (spontaneous diuresis?) (Same patient as Table II)

Fig 6e Anterior view of the same patient twelve months after his appearance in Figure 6c and d Further reduction in ascites

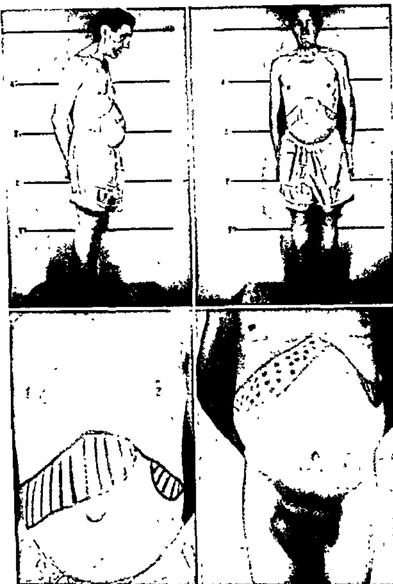


Fig 6f Anterior view of the torso of a patient with alcoholic, portal cirrhosis, gynecomastia, hepatosplenomegaly pectoral alopecia, esophageal varices, ascites, inguinal hernia and scrotal edema

tary fat in the management of cirrhosis and ascites. A moderate intake of fat is not injurious to the liver and also increases the palatability of a sodium-restricted diet. Calcium glutamate and ammonium glutamate, if the latter is employed with discretion, are two flavoring agents recommended to improve the taste of low-sodium diets. The diet recommended in the management of cirrhosis and ascites and edema should provide adequate but not superfluous increments of vitamins and methionine. Whereas adjunctive therapy with lipotropic agents is unnecessary, it is conventional to augment the diet usually with Brewer's Yeast USP, 4 tablets three to four times daily, and a therapeutic vitamin USP twice daily. Injectable vitamins as a replacement for oral vitamins is indicated in critical patients. A recommended diet can be found in Chapter 17. A trial of corticosteroid therapy has been reported to be of value in the diuresis of patients with cirrhosis and ascites.[16,39,94]

Various types of diuretics have been advocated for the urinary excretion of sodium and water in cirrhosis with ascites and edema. In contrast to the usual patients with congestive heart failure, cirrhotic patients with ascites and edema are relatively more resistant to diuretic therapy. The main diuretic drugs employed in this condition are the mercurial diuretics, cation-exchange resins, various new non-mercurial diuretics, and salt-poor serum albumin. The mercurial diuretics that are used in the treatment of cirrhosis with ascites or edema are as follows: parenteral medications such as mercaptomerin (Thiomerin®), mercumatilin (Cumertilin®), meralluride (Mercuhydrin®), mercuzanthin (Mercurophylline®), mersalyl (Salyrgan®), and the oral diuretics such as chlormerodrin (Neohydrin®) (Table IV). The principal function of these diuretics is essentially to decrease tubular reabsorption of sodium by the inhibition of SH-activated enzyme systems. As a result of intensive mercurial diuresis there is a greater loss of chloride than bicarbonate *from the extracellular fluid, which tends to produce* a hypochloremic alkalosis.[71,111,198,237] The oral administration of calcium chloride has been recommended to correct the inevitable hypochloremia as the result of mercurial diuresis and to perpetuate diuresis in those fast to mercurials.[197,213,216] Hypokaliemia may occur in addition to hyponatremia particularly if rigid dietary restriction of

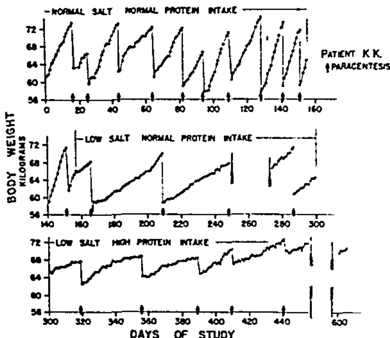


FIG 7 Long term study of weight changes in a patient with cirrhosis and ascites studied for 600 days Numerous abdominal paracentesis occurred when patient subsisted on a normal sodium, normal protein diet, the accumulation of ascites was diminished when sodium intake reduced to 33 mEq /day and there was no increase in body weight Further reduction in ascites and gain in body weight when continued restriction of sodium and high protein diet was administered (Courtesy, Kark, R M—Liver Disease, A Ciba Symposium—Klakiston, 1951)

sodium is recommended [114] These electrolyte abnormalities may particularly endanger the elderly cirrhotic with benign nephrosclerosis [209] The potentiation of the effects of mercurial diuretics by the oral administration of ammonium chloride is hazardous because of producing ammonia intoxication and coma Because mercury is a potential hepatotoxic agent, medication containing this element should not be employed indiscriminately for patients with cirrhosis In addition to depletion of extracellular fluid and elec-

TABLE IV

CLINICAL AND LABORATORY FINDINGS OF A 51 YEAR-OLD MALE WITH DECOMPENSATED ALCOHOLIC PORTAL CIRRHOSIS

Clinical Manifestations	*Date* 1952	1953	1954	1955
Bodyweight, lb	194	170	169	173
Emaciation	3+	1+	0	0
Jaundice	+	+	0	0
Ascites	3+	1+	0	0
Edema	2+	1+	0	0
Alopecia	+	+	+	+
Spider angioma	+	+	+	+
Palmar erythema	+	+	+	+
Testicular atrophy	+	+	+	+
Hepatomegaly	0	0	1f	1f
Splenomegaly	0	3f	3f	3f
Laboratory Data				
Bilirubin, serum, mg per 100 cc	0.6/2.0	0.9/3.2	0.46/2.39	0.2/1.9
BSP retention % 45 min	32	41	34	19
Cholesterol, serum, mg per 100 cc	—	182	204	210
Cholesterol [illegible]	—	62	137	143
[illegible]	4+	2+	0	1+
[illegible]	3.7	8.4	4.0	3.6
[illegible]	32	39	67	100
[illegible]	+	+	+	(size reduced)
[illegible]	9.4	8.8	14.1	13.6
[illegible]	3.83	3.40	4.14	4.26
[illegible]	5550	4100	4000	6200
[illegible]	286,000	—	367,000	422,000
Sedimentation rate (Westergren)	26	8	10	6
Albumin, serum, gm per 100 cc	3.3	2.5	4.7	4.4
Globulin, serum, gm per 100 cc	2.6	1.1	1.9	2.3
Course	Pleural effusion	Asymptomatic gynecomastia, Clubbed fingers		
Treatment	Bedrest [illegible]			

trolytes and fluid in cirrhosis, further untoward reactions from these drugs are mercury resistance, gastrointestinal irritation, systemic mercury poisoning, allergic cutaneous reactions, renal shutdown, thromboembolic complications, digitalis intoxication and, rarely, ventricular fibrillation Despite these possible inherent complications from the use of mercurial diuretics in patients with cirrhosis and ascites and edema, these medications are administered more frequently and effectively than any other diuretic in association with sodium-restricted diets.

Cation exchange resins have had restricted use in the past for the treatment of edema and ascites in patients with cirrhosis. They are actually useless and unnecessary if the patient is properly adhering to a sodium restricted diet. The most acceptable resins are the acid carboxylic or sulfonic resins containing potassium instead of an ammonium cation because of inherent ammonia intoxication. Resins act by exchanging the H-ion for sodium in the gastrointestinal tract producing an acidosis which is compensated for by potassium. The therapeutic results of this type of diuretic therapy in patients with cirrhosis. One is acetazolamide (Diamox®), a carbonic agents allow the cirrhotic to increase his oral intake of sodium and improve the flavor of food. However, they may induce certain complications such as anorexia, nausea, vomiting, diarrhea, hypocalcemia, hypokaliemia, hyperchloremia, acidosis and hepatic coma. The large dose of this drug, 45-60 gm. daily in divided doses between meals, may be objectionable for some patients.

There are various non-mercurial oral diuretics that have been recently employed in the management of ascites and edema in patients with cirrhosis. One is acetazolamide (Diamox®), a carbonic-anhydrase inhibiting agent and is mentioned only to condemn its use in any case of cirrhosis. It has been observed that the therapeutic administration of this drug induces hepatic coma, though its frequent use testifies that this is an uncommon complication.[15,121,186,215,225] Aminometradine (Rolicton®) and aminoisometradine (Mictine®) are oral diuretics which are relatively nontoxic and have been recognized to have limited value in initiating diuresis in cirrhosis, but may be effective in maintaining diuresis like chloromerodrin (Neohydrin®) and reduce the necessity of frequent parenterally administered diuretics.[261,262] Chlorothiazide, a newer nonmercurial sulfamyl diuretic agent, has aroused considerable interest by its antihypertensive and chloruretic and natruretic effects.[92,93,135,222,229,270] It is a moderate carbonic anhydrase inhibitor in vitro and also, presumably, partially blocks the renal tubular absorption of sodium and chloride. It has been found to be effective in treating ascites due to cirrhosis, but produces a marked urinary loss of potassium and hypokaliemia. Hepatic coma has been produced by chlorothiazide and prevented by antibiotics.[153,224]

Concentrated salt-poor serum albumin has been advocated as

replacement therapy in the treatment of patients with cirrhosis and ascites and edema It may correct hypoalbuminemia, increase the osmotic pressure of the plasma, and maintain normal capillary permeability by restoring the endothelial content of protein [7,86 123,127, 134,201 232 260] On the other hand, several groups have demonstrated that salt-poor serum albumin is generally ineffective or, at best, has only temporary therapeutic value.[86,186 260] Patek has concluded that there is increased renal blood flow and glomerular filtration probably as the result of increased plasma volume when serum albumin is administered in cirrhotics. The recommended initial dosage is 25 gm per 100 cc daily with an increase to 50 gm daily thereafter (Fig 8) As much as 750 to 1,000 gm has been employed to effect adequate diuresis, but invariably these enormous and prohibitively expensive amounts signify ominous therapeutic failure Diuresis after the administration of salt-poor serum albumin may be sudden or prolonged Pulmonary edema, fever, nausea, vomiting, mobilization of edema rather than ascitic fluid, precipitation of hemorrhagic esophageal varices and rarely even hepatic coma and shock are some of the disadvantages and complications of this treatment, which may outweigh the therapeutic benefit.

Abdominal paracentesis is one of the therapeutic procedures of choice when ascites in a patient with cirrhosis causes marked uncomfortable abdominal distention and creates labored respiration If abdominal paracentesis is employed indiscriminately and too hastily, certain complications arise obscuring the initial problem (Fig 9). These are peritoneal hemorrhage, hepatic coma, hypovolemia, shock, infection, delayed healing, perforation of peptic ulcer, penetration of an abdominal viscus and loss of albumin and sodium into ascitic fluid with subsequent reaccumulation of ascites [99,130,180,226] The latter complication may initiate a vicious cycle of ascites and paracentesis This is well appreciated and tends to make *abdominal paracenteses a restricted procedure* In an effort to elevate the plasma osmotic pressure and lessen repeated paracenteses, Armstrong recommends the simultaneous use of salt-poor serum albumin. Exfoliative cytological examination of ascitic fluids may reveal hepatic cells in patients with cirrhosis [152]

Other surgical procedures have been recommended for the re-

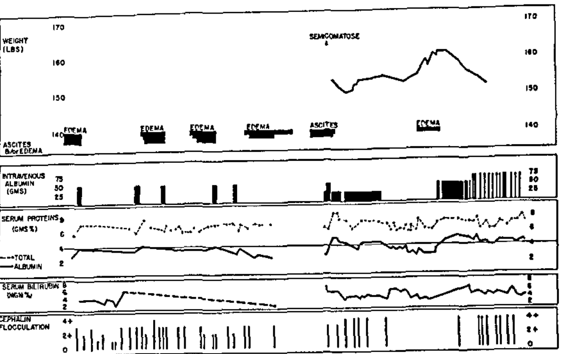


Fig. 8. Effect of the administration of salt poor albumin in a patient with portal cirrhosis and ascites. Following each course of therapy with albumin, diuresis occurred, and, upon cessation, the serum albumin value declined; values of serum bilirubin and cephalin cholesterol flocculation remain unaltered. (Courtesy, Post, Rose, and Shore—Arch. Int. Med.—June, 1951.)

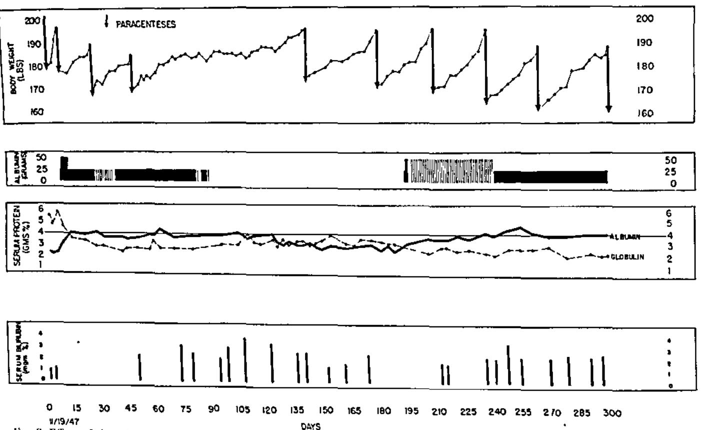


FIG. 9 Effect of the administration of salt poor serum albumin in a patient with portal cirrhosis and ascites Widening of paracentesis interval accompanied initial course of albumin therapy. (Courtesy, Post, Rose, and Shore—Arch. Int Med—June, 1951)

lief of intractable ascites in patients with cirrhosis. Talma in 1898 and Morison in 1912 independently performed an omentopexy.[174, 241] This surgical procedure was devised to create adhesions between the parietal and visceral peritoneum to establish collateral circulation.[174,241] The significantly high postoperative mortality and therapeutic failures make this procedure only of historical interest. In 1946 Crosby and Cooney described an operation in which a modified Murphy button was inserted into the abdominal wall connecting the peritoneal cavity with the subcutaneous tissue causing resorption of ascitic fluid.[59] The results of this treatment are unpredictable. The buttons invariably become plugged with fibrin or omentum or become infected or a pseudoperitoneal cavity may develop. A plastic tube has been improvised and placed in the anterior abdominal wall for repeated abdominal paracenteses.[157] Lord has recommended a modification of this operation by resecting fascia to expose the lymphatics in the abdominal muscles and also removal of redundant omentum to prevent plugging of the button.[145] Ileo-entectropy, isolation, eversion and mobilization of a segment of ileum to the parietal peritoneum has been proposed to relieve ascites, but clinical experience with this operation is currently limited.[151]

Generally, ascites has been considered a contraindication for a portal shunt operation in patients with cirrhosis and esophageal varices. There are, however, a few reports of cases in which shunt procedures were performed following which ascites did not recur.[27,80,131,132,259] Madden and his co-worker considered that irreversible ascites in patients with cirrhosis was due to an obliterative fibrosis of the intrahepatic systemic venous bed.[153] They described a method to produce vascular collaterals of the liver between the portal and systemic veins by applying magnesium trisilicate powder to abraded areas over the superior surface of the liver and inferior surface of the diaphragm. Surgical ligation of the hepatic and splenic arteries for the treatment of esophageal varices and also ascites has had contradictory results (Chapter 16).[21,22,219] Refractory ascites has been treated successfully by bilateral adrenalectomy in a patient with postnecrotic cirrhosis.[102]

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Chapter 16

HEPATIC INSUFFICIENCY

INTRODUCTION

HEPATIC INSUFFICIENCY indicative of hepatocellular damage is commonly associated with such conditions of the liver as viral or toxic hepatitis, abscesses, granulomas, infiltrative and metabolic diseases, bacterial diseases, neoplasms, polycystic disease of the liver and cirrhosis. On the other hand, when the term "latent cirrhosis" is employed this means that the stigmata and symptoms of hepatic insufficiency are absent. The clinical picture of hepatic insufficiency in patients with cirrhosis may be variable, nonspecific or predominated by one of the following syndromes or a combination of some or all of them. These include: (1) hepatocellular jaundice; (2) fever, chills and malaise, (3) gastrointestinal symptoms, such as, nausea, vomiting, abdominal pain, diarrhea, constipation, distaste for food, malnutrition, impaired appetite and loss of weight; (4) neuropsychiatric states, such as, psychoneurotic manifestations, peripheral neuritis, headaches and impending or terminal hepatic coma; (5) hematologic manifestations, such as, hemorrhage from various sites, hypersplenism and anemias of various types. Many clinicians include ascites, edema and portal hypertension in the category of symptoms of hepatic insufficiency. Their significance in cirrhosis has been alluded to in Chapters 14 and 15. The manifestations of hepatic insufficiency may vary from minor abnormalities in various hepatic function tests to hepatic coma [141, 270,351,471-474]. Certain biochemical tests are employed which may demonstrate an abnormality of a particular function of the liver in patients with cirrhosis. These include biochemical hepatic abnormalities referrable to: (1) bile pigment metabolism, (2) excretory function, (3) detoxification and conjugation, (4) metabolism of protein, carbohydrate and fat, (5) specific enzymes, (6) storage of minerals and vitamins; (7) regulation of hormones; and (8) water and electrolyte metabolism (Chapter 15).

The complexity of the subject of hepatic insufficiency is testified

to by the fact that no single hepatic function test is indicative of the capacity of the liver, that the liver probably has several hundred specific physiological activities, and that only rough correlation exists between morphological and biochemical alterations in diseases of the liver (Fig. 1). It is necessary, therefore, to analyze available clinical and biochemical data closely in patients with cirrhosis and hepatic insufficiency, and to anticipate future physiological investigations necessary and indispensable in the interpretation of hepatic physiology

BIOCHEMICAL MANIFESTATIONS OF HEPATIC INSUFFICIENCY

The following physiological abnormalities indicative of hepatic insufficiency will be discussed with reference to cirrhosis The reader is referred to the standard texts on diseases of the liver for detailed descriptions of normal hepatic function and various hepatic function tests in health and hepatic disease.

Bile-Pigment Metabolism

Abnormalities in bile secretion occur in cirrhosis and are associated with certain symptoms and physical findings. Impaired bile-pigment metabolism in cirrhosis, producing increased total serum bilirubin, may reflect either hepatocellular damage, obstruction of either the intrahepatic or extrahepatic bile ducts, or, in the case of secondary hypersplenism, increased hemolysis of erythrocytes Consequently, hepatocellular, obstructive (regurgitation), or hemolytic (retention) jaundice may be a clinical feature of cirrhosis Determination of the fractionated serum bilirubin aids in the differentiation of these types of jaundice. Direct-reacting bilirubin consists of bilirubin usually coupled with two molecules of glucuronic acid, although small amounts of monoglucuronide may also exist [15,51,52 234,235 537-539,613,679] Indirect-reacting bilirubin is free, unconjugated bilirubin An enzyme, glucuronyl transferase, which

glucuronide), or that which gives a prompt reaction biochemically within one minute, is regurgitated from the intrahepatic bile ducts. [15,163,234,235] Using this method, the normal value is 0 to 0.25 mg /100

cc. of blood.[57] The delayed or indirect serum bilirubin as determined at thirty minutes, the normal value being 0.25 to 1.0 mg./100 cc. of blood, is an apparent indication of breakdown of hemoglobin by the reticuloendothelial system including the Kupffer

PHYSIOLOGY OF THE LIVER

I PROTEIN METABOLISM

II CARBOHYDRATE METABOLISM

III FAT METABOLISM

V OTHER FUNCTIONS

IV PRODUCTION AND SECRETION OF BILE

Fig. 1. (Courtesy, Parke, Davis & Co.)

cells in the liver Elevation of the indirect or delayed-reacting serum bilirubin is observed in hemolytic jaundice and progressive hepatocellular jaundice, in which case the Kupffer cells accumulate bilirubin which the damaged cell is unable to excrete. High values of direct serum bilirubin are found in cases of primary or secondary biliary cirrhosis, indicative of biliary tract obstruction, postnecrotic cirrhosis, and in cirrhosis of other types, particularly after an alcoholic debauch or terminally, presumably due to parenchymal damage. Surprising to the neophyte, the highest direct and total serum bilirubins are not found in obstructive jaundice but in hepatocellular jaundice, in cases of viral hepatitis and in cases of cirrhosis, particularly the postnecrotic variety. The value of a determination of total rather than fractionated serum bilirubin, or an icterus index in any case of jaundice, is misleading and antiquated One is impressed with the lack of correlation between histological evidence of hepatic damage and the amount of fractionated serum bilirubin, on the one hand, and the nonspecificity of this test in patients with cirrhosis on the other.[532,659 690] In patients with established portal cirrhosis, persistent hepatocellular jaundice is an ominously poor prognostic sign

There are other biochemical abnormalities indicative of disordered bile-salt metabolism in patients with cirrhosis. Bilirubinuria, as detected by either the foam test, methyline blue, Harrison Spot or the Franklin test may be found in cirrhosis associated with obstructive or hepatocellular jaundice. The two-hour quantitative urine urobilinogen (normal less than one Ehrlich unit or 0 25 mg) and twenty-four hour quantitative urinary (normal, 0 5 to 4 0 mg.) and fecal urobilinogen (normal, 100 to 300 mg) have diagnostic usefulness in determining the type of jaundice in patients with cirrhosis[621 637-641,645,651] Watson has also noted an increase in type 3 urinary coproporphyrin in portal cirrhosis among alcoholics[430 646 652]

Excretory Function

This specific function of the liver becomes impaired in cirrhosis even when a minor grade of hepatic insufficiency exists Normally, the liver excretes sodium bilirubinate, cholesterol, fatty acids, lecithin, lipids, sodium glycocholic and tauracholic acids,

which are the bile salts, and various drugs that a patient may have been administered such as the chemotherapeutic and antibiotic agents. The excretory function of the cirrhotic liver is determined by its ability to excrete foreign dyes such as sodium sulfobromophthalein (BSP), rose bengal, radioactive rose bengal, and Azorubin S.[71,236,255,441,514,515] The most practical and sensitive of this group, which indicate hepatic dysfunction in patients with cirrhosis, are the bromsulfalein and, more recently, the radioactive rose bengal tests.

The bromsulfalein test usually employed requires the intravenous administration of 5 mg. of this dye/kilogram body weight and determination of the amount of dye retained in the blood at the end of forty-five minutes.[231,255,595,821] The dye is picked up by the hepatic cells and excreted by the bile ducts, and abnormal retention is a sensitive test of hepatocellular damage, biliary stasis and circulatory impairment in the liver. Retention of bromsulfalein dye in normal individuals varies between 0 and 5 per cent. There are certain factors, however, that influence the clearance of the dye from the liver and may induce abnormal retention. These are fever, posture, exercise, congestive heart disease, shock, surgical operations, diabetes mellitus, obesity, hyperthyroidism, Cushing's disease, gallbladder disease, obstruction of the common bile duct, biliary fistula, malaria, chronic ulcerative colitis, infections, jaundice, and the factor of time; i.e., in excess of sixty minutes due to the enterohepatic circulation or extrahepatic removal of the dye.[50,69,73,120,140,191,271,286,353,361,465,595,687a] A significant diagnostic limitation of the test occurs during the presence of jaundice because of interference with colorimetric determination, but Zieve and his coworkers have devised a table for correction of bromsulfalein retention in jaundiced patients.[691] Retention of bromsulfalein dye is found regularly in patients with cirrhosis, but there is only fair correlation with morphological damage of the liver.[467,471,472,474,478,519,521] Decreased retention of dye usually signifies improvement in hepatocellular damage, whereas prolonged low-grade retention may persist in spite of clinical and other laboratory improvement in patients with cirrhosis. Patients with hemochromatosis, hepatolenticular degeneration, postnecrotic cirrhosis, or treated portal cirrhosis, for example, may have normal retention of bromsulfalein

dye despite established morphological evidence of cirrhosis In many of these conditions cirrhosis may be in an early stage or healed, indicating reasonably normal hepatocellular function. No correlation exists between this *test and evidences of portal hypertension* or ascites in patients with cirrhosis Prolonged retention of the dye in cirrhosis also *has therapeutic implications as observed in cirrhotics* who do not follow prescribed treatment.

The rose bengal and azorubin S hepatic function tests have not been employed generally because they are less sensitive and far *more impractical than the bromsulfalein test. The radioactive* (I^{131}-tagged) rose bengal hepatic uptake-excretion test has been *recommended for patients with jaundice when the result of the* bromsulphalein test is unreliable [575,599,600]

Detoxification and Transformation

The liver has a particular function of detoxifying, oxidizing and conjugating many substances and excreting them into the bile ducts *These include* various substances as narcotics, barbiturates, chlorylhydrate, cincophen, hormones, quinine, histamine, salfonamides, amino acids and benzene derivatives. *The Kupffer cells* are phagocytic and remove bacteria and colloid particles The diseased liver, therefore, has a reduced ability *to detoxify* many drugs employed in the treatment of cirrhosis, namely, morphine, meperidine, methadon and the barbiturates

Hepatic function tests which depend upon the process of transformation *in the liver are, in particular, the oral or intravenous* hippuric acid synthesis, paraminohippurate synthesis, benzoylglucuronate *excretion*, cinchophen-oxidation *test, nicotinamide-*methylation test, and the cinnamic acid test [144,325,420,483,484,488,489,491,500,507,519,520,571,572,589,601] *The hippuric acid test has had more* popular use It is employed less currently now because of technical difficulties, *its dependence on normal renal function, reported abnormal renal excretion of hippuric acid in psychiatric cases*, and hyperexcretion *of hippuric acid in some patients with minimal* hepatic damage, senility, pregnancy, malnutrition, hyperthyroidism, carcinomatosis, *obstructive jaundice and congestive heart* failure. The test is based on the fact that sodium benzoate is conjugated *in the liver with glycine to form hippuric acid*, which is

excreted by the liver. Abnormal hippuric acid tests are not found consistently in patients with cirrhosis Normal hippuric acid synthesis may occur in cirrhosis making this test technically insensitive.

Protein Metabolism

The synthesis of protein is one of the most important functions of the liver. Evidences of this are demonstrated by abnormalities in the amounts of prothrombin, fibrinogen, albumin, globulin and certain proteinases in the serum in patients with hepatic disease, regeneration of the liver after hepatitis or partial hepatectomy, synthesis of protein from amino acids experimentally, and transaminization or deaminization of amino acids, the latter resulting in the formation of urea. Proteins acting as a reservoir constitute the majority of the dry weight of the liver, and in hepatic disease or malnutrition their content diminishes rapidly [2, 42, 44, 213, 214, 222, 259, 259, 340–342, 413, 404, 431, 434, 650] Hepatic synthesis and degradation of proteins characterize normal protein metabolism The essential amino acids play a predominant role in the synthesis of protein. Their deficiency may produce negative nitrogen balance, specific biochemical disturbances, retention of body fluid, various hepatic, cerebral or arterial lesions, mental deficiency, intercurrent infections and deterioration of the body Severe protein malnutrition is a regular accompaniment of cirrhosis, particularly in the alcoholic patients. This is observed by. (1) reduced food intake; (2) impaired digestion, (3) malabsorption, (3) altered intermediary metabolism; (5) increased excretion, and (6) hormonal disturbances [139, 443, 620] Cirrhosis is associated with impaired synthesis of protein particularly albumin, and certain biochemical tests have been employed diagnostically to determine abnormal metabolism of protein in the diseased liver These are, principally determinations of fractionated serum proteins, the flocculation and turbidity tests cephalin-cholesterol flocculation, thymol turbidity and flocculation, zinc sulfate turbidity, gamma-globulin turbidity, plasma fibrinogen, and less popular tests, such as, the colloidal gold or colloidal red test, Takata-Ara reaction, erythrocyte sedimentation rate, prothrombin time, serum and urinary amino acids, amino acid and methionine tolerance tests, and blood urea nitrogen and nonprotein nitrogen. Cirrhosis may be reflected by abnormalities of the various protein fractions

dye despite established morphological evidence of cirrhosis. In many of these conditions cirrhosis may be in an early stage or healed, indicating reasonably normal hepatocellular function. No correlation exists between this test and evidences of portal hypertension or ascites in patients with cirrhosis. Prolonged retention of the dye in cirrhosis also has therapeutic implications as observed in cirrhotics who do not follow prescribed treatment.

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Detoxification and Transformation

The liver has a particular function of detoxifying, oxidizing and conjugating many substances and excreting them into the bile ducts. These include various substances as narcotics, barbiturates, chlorylhydrate, cincophen, hormones, quinine, histamine, sulfonamides, amino acids and benzene derivatives. The Kupffer cells are phagocytic and remove bacteria and colloid particles. The diseased liver, therefore, has a reduced ability to detoxify many drugs employed in the treatment of cirrhosis, namely, morphine, meperidine, methadon and the barbiturates.

Hepatic function tests which depend upon the process of transformation in the liver are, in particular, the oral or intravenous hippuric acid synthesis, paraminohippurate synthesis, benzoylglucuronate excretion, cinchophen-oxidation test, nicotinamide-methylation test, and the cinnamic acid test.[144 325 426 483 454 486 459, 491 506 507 519 520 571 572, 690 691] The hippuric acid test has had more popular use. It is employed less currently now because of technical difficulties, its dependence on normal renal function, reported abnormal renal excretion of hippuric acid in psychiatric cases, and hyperexcretion of hippuric acid in some patients with minimal hepatic damage, senility, pregnancy, malnutrition, hyperthyroidism, carcinomatosis, obstructive jaundice and congestive heart failure. The test is based on the fact that sodium benzoate is conjugated in the liver with glycine to form hippuric acid, which is

2, beta, beta-2 and gamma and gamma-2, globulins, fibrinogen, and lipoproteins.[132 233 301 321 346 362 363 390 392 505 507-509] However, electrophoretic patterns usually do not distinguish the type of cirrhosis, and, therefore, their diagnostic value is questionable except in patients with primary biliary cirrhosis or cirrhosis with hypergammaglobulinemia (Table I) (Fig. 2).[117,172 206 322 336 438 462,468 471,474 503, 505 507-509 594 595 605] A persistent combination of decreased serum albumin and elevated serum gamma globulin denotes a poor prognosis, whereas improvement in the level of serum albumin suggests satisfactory convalescence. The level of alpha globulin in the serum obtained from patients with cirrhosis does not have the diagnostic significance of the beta or gamma fractions. Elevation of the beta globulin fraction which migrates with the lipoproteins may be observed in primary biliary cirrhosis with or without xanthematosis and hyperlipemia.

Treatment	A/G		Gm per 100 cc Serum			
			α^1	α^2	β	γ
Normal	1 0 1.5 (NaSO⁴)	3 8 4 6 Albumen	0.2 0.5 Globulin	0.5 1.2 Globulin	0 75 1.3 Globulin	1 1 1 7 Globulin
Dietary	0 8	3 0	0.2	0.5	0.9	2.3
Esophageal tamponade	0 6	2 6	0.3	0 4	1.2	3.3
Dietary	0 8	3 0	0.3	1.2	1.3	1 6
Dietary	0 4	2.3	0.5	0 7	1.5	2 4
	0.5	2.8	0 4	0 7	1.5	2.5
Dietary	1 0	3.3	0.5	0 7	1.3	1 8
10 days before	0 4	2.3	0 3	0 4	1.3	3.2
Portacaval shunt	0 7	2.9	0 4	0.5	1 0	2.5
9 days later	0 6	2 4	0 3	0 4	0 8	2 6
Dietary	0 3	1 7	0.3	0 6	1 0	5.3
Dietary	0 8	3.5	0 4	0 4	1 0	2 7
Dietary	1 1	4.2	0.3	1 0	0 9	1.6
Multiple phlebotomy	0 6	2 7	0.3	0 4	0 9	2 9
BAL Injections	1 1	3 7	0.3	0.5	0.9	1.6
1 day before Spleno renal shunt	1.2	3 4	0 4	0 6	0 9	1 0
Splenorneal shunt	1.0	2 9	0 4	0 7	0 9	0 9
16 days later	0 8	3 7	0.3	1.5	1.1	1.5
Dietary	0 9	3.3	0 3	0.5	1.2	2 0
Dietary	0 8	3.2	0 3	0 6	0 7	2.3
Steroids & Dietary	0.2	2.0	0 3	0 4	0 8	8 1
Dietary & Rest	1 01	4 0	0 3	0 7	1 1	1 8
Dietary	1 0	4.5	0 3	0.8	1 1	1 8
Dietary	0.5	2.2	0 4	0.5	3 3	0 6
Dietary	0 6	3 2	0 4	1 0	1.2	2 0
Choledochojejunostomy	0.5	2 1	0 3	0 8	0 8	1 7
Choledocholithotomy	0 9	3 4	0 5	1.2	1 1	1 0
Choledochojejunostomy	0.8	2.5	0 4	0 8	0 9	1.2
Gastroentertostomy	1 0	3 9	0 4	1 1	1.2	1 0

in the serum, such as, hypoalbuminemia, hypergamma globulinemia, hypoprothrominemia, and in severe active cirrhosis, hypofibrinogenemia. Hypoalbuminemia in cases of cirrhosis has been proven by albumin I [131] studies to be the direct result of decreased synthesis of albumin by the diseased liver. Eisenmenger and his co-workers have called attention, furthermore, to the plasmapheretic effect of increased sodium intake by augmenting ascites on further decreasing level of serum albumin.[174] They found that the progressive loss of serum albumin into ascitic fluid did not appear to stimulate further hepatic synthesis of albumin. More accurate and elaborate than the standard Howe or Wolfson-Cohn techniques for biochemical determination of serum protein fractions is electrophoresis introduced in 1937 by Tiselius [292,283,808,641] Electrophoresis of serum proteins enables one to differentiate *quantitatively the various proportions of albumin, alpha-1, alpha-*

TABLE I
ELECTROPHORETIC DETERMINATIONS OF SERUM PROTEINS IN VARIOUS TYPES OF CIRRHOSIS

Case No	*Type of Cirrhosis*	*Complication*
1	Alcoholic portal	Ascites
2	Alcoholic portal	(Fatal esophageal hemorrhage)
3	Alcoholic portal	Ascites
4.	Alcoholic portal	Ascites
5	Alcoholic portal	6 mos after treatment
6	Alcoholic portal	None
7	Cryptogenic portal	Esophageal hemorrhage
	Cryptogenic portal	Esophageal hemorrhage
	Cryptogenic portal	Esophageal hemorrhage
8	Posthepatitic (?) portal	Hepatic insufficiency
9	Portal, chlorpromazine hepatitis	None
10	Hemochromatosis	None
11	Hemochromatosis	Ascites
12.	Hepatolenticular degeneration	None
13	Postnecrotic	Esophageal hemorrhage
	Postnecrotic	Esophageal hemorrhage
	Postnecrotic	Esophageal hemorrhage
14	Postnecrotic	None
15	Postnecrotic	Hypersplenism
16.	Postnecrotic	Diss. lupus erythematosis
17	Cholangiolitic hepatitis	None
18	Primary biliary	None
19	Primary biliary	Xanthomatosis
20	Primary biliary	Xanthomatosis
21	Secondary biliary	None
22	Secondary biliary	None
23	Secondary biliary	Xanthomatosis
24	Obstructive jaundice, neoplastic	None

2, beta, beta-2 and gamma and gamma-2, globulins, fibrinogen, and lipoproteins [132,213,303,321,340,342,363,380,382,503,507-509] However, electrophoretic patterns usually do not distinguish the type of cirrhosis, and, therefore, their diagnostic value is questionable except in patients with primary biliary cirrhosis or cirrhosis with hypergammaglobulinemia (Table I) (Fig. 2).[117,172,206,322,336,438,462,468,471,474,503,505,507-509,534,535,565] A persistent combination of decreased serum albumin and elevated serum gamma globulin denotes a poor prognosis, whereas improvement in the level of serum albumin suggests satisfactory convalescence The level of alpha globulin in the serum obtained from patients with cirrhosis does not have the diagnostic significance of the beta or gamma fractions. Elevation of the beta globulin fraction which migrates with the lipoproteins may be observed in primary biliary cirrhosis with or without xanthematosis and hyperlipemia.

Treatment			Gm per 100 cc Serum			
	A G		*α¹*	*α²*	*β*	*γ*
	1 0 1.5	3.8 4.6	0.2-0.5	0.5 1.2	0 75-1.5	1 1 1 7
Normal	*(NaSO⁴)*	*Albumen*	*Globulin*	*Globulin*	*Globulin*	*Globulin*
Dietary	0 8	3 0	0.2	0.5	0 9	2.3
Esophageal tamponade	0 6	2 6	0.3	0 4	1.2	3 3
Dietary	0.8	3.0	0.3	1.2	1.3	1 6
Dietary	0 4	2.3	0.5	0 7	1.5	2 4
	0.5	2.8	0 4	0 7	1.5	2.5
Dietary	1 0	3.3	0.5	0 7	1.3	1 8
10 days before	0 4	2.3	0.3	0 4	1.3	3.2
Portacaval shunt	0 7	2 9	0 4	0.5	1 0	2.5
9 days later	0 6	2 4	0.3	0 4	0 8	2 6
Dietary	0.3	1 7	0 3	0 6	1.0	5.3
Dietary	0 8	3.5	0 4	0 4	1.0	2 7
Dietary	1 1	4.2	0.3	1.0	0 9	1 6
Multiple phlebotomy	0 6	2 7	0.3	0 4	0 9	2 9
BAL Injections	1 1	3 7	0 3	0.5	0 9	1 6
1 day before Spleno renal shunt	1.2	3 4	0 4	0 6	0 9	1 0
Splenorneal shunt	1.0	2.9	0 4	0 7	0 9	0 9
16 days later	0 8	3 7	0.5	1.5	1 1	1.5
Dietary	0 9	3.3	0 3	0.5	1.2	2 0
Dietary	0 8	3 2	0 3	0 6	0 7	2 3
Steroids & Dietary	0.2	2 0	0.3	0 4	0 8	8 1
Dietary & Rest	1.01	4 0	0 3	0 7	1 1	1 8
Dietary	1.0	4.5	0 3	0 8	1 1	1 8
Dietary	0.5	2.2	0 4	0 5	3.3	0 6
Dietary	0 6	3.2	0 4	1 0	1.2	2 0
Choledochojejunostomy	0.5	2 1	0 3	0.8	0 8	1 7
Choledocholithotomy	0 9	3 4	0 5	1.2	1 1	1 0
Choledochojejunostomy	0 8	2.5	0.4	0 8	0 9	1.2
Gastroenterostomy	1 0	3 9	0 4	1 1	1 2	1 0

Elevation of the gamma globulin in cirrhosis reflects stimulation of the reticuloendothelial system and plasma cells. It is a common biochemical feature of any hepatic disease especially in active advanced cirrhosis in young girls and in postnecrotic cirrhosis. In these cases, extremely high levels are determined. The cause of hypergammaglobulinemia in patients with cirrhosis is unknown and apparently it is not produced by the hepatic cells (Table II).

TABLE II

CLINICAL AND LABORATORY DATA OF A 23 YEAR FEMALE WITH POSTNECROTIC CIRRHOSIS, HYPERGAMMAGLOBULINEMIA, AND POSITIVE PLASMA L. E. PHENOMENON

Clinical Manifestation	*1953*	*7-5-55*	*9-10-55*	*12-19-55*	*7-17-56*
Body weight, lbs	0	114	116	120	125
Jaundice	0	+	+	+	0
Arthritis	+	+	+	+	0
Oral temp (F)	*98.6°*	*98.6°*	*101.5°*	*99°*	99°
Acne	0	+	+	+	+
Dyspnea	0	0	+	0	+
Ascites	0	0	+	0	0
Edema	0	0	0	+	+
Diaphoresis	0	0	+	0	0
Abdominal pain	0	+	+	+	+
Epistaxis	0	+	+	+	0
Heptaomegaly	0	2f	2f	2f	2f
Splenomegaly	0	1f	2f	2f	2f
Weakness	+	+	+	+	+
Pharyngitis	0	+	+	0	0
Spider angioma	0	+	+	+	+
Laboratory Data					
Bilirubin serum, D/T, mg per 100 cc		1.7/2.9	2.8/4.4	—	2.6/4.5
Alk. phosphatase, plasma Bodansky units		—	4.0	—	—
BSP retention % retention 45 min		34	26	—	7
Cephalin flocculation		3+	3+	3+	4+
Thymol turbidity, units		22.4	21	—	23.2
Zinc sulfate turbidity		29	27.5	—	43.2
Sedimentation rate (Westergren)		102	126	100	90
Prothrombin time %		49	14	—	—
False positive serology		+	+	+	+
Hemoglobin blood, gm per 100 cc		10.9	8.5	13.3	—
RBC×10⁶ per cu. mm		3.40	—	—	4.25
WBC per cu. mm		5500	4300	8500	—
Platelets per cu. mm		680,000	182,000	220,000	383,000
Albumin, serum, gm per 100 cc		2.6		2.8	—
Globulin, serum, gm per 100 cc		6.5		6.6	—
Treatment:	200 gm Protein, 500 gm Carbohydrate, Fat ad lib Diet, vitamins, Vit. K, Bed rest		Diet & Prednisone	Diet & Prednisone 20 mg/day	Diet & Prednisone

PAPER ELECTROPHORETIC ANALYSIS OF SERUM

DIRECTION OF MIGRATION ——

SERUM PROTEINS

COMPONENT	Adult Normals	FOUND	SUMMARY:
Total Protein	6.2-8.5 gm. %	7.5 gm %	Low albumin, alpha₂ globulin and A/G ratio. High gamma globulin.
% of total protein: Albumin	56-70	30	
Globulins			
Alpha 1	2-5	4.6	
Alpha 2	7-11	5.7	
Beta	8-14	16.7	
Gamma	9-21	41.0	
A/G ratio	1.1-2.4	0.43	

FIG 2 Paper electrophoretic patterns of serum proteins in types of cirrhosis a Portal cirrhosis cryptogenic, impending hepatic coma, hemorrhage from esophageal varices, ascites.

PAPER ELECTROPHORETIC ANALYSIS OF SERUM

DIRECTION OF MIGRATION ——

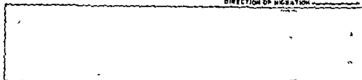
SERUM PROTEINS

COMPONENT	Adult Normals	FOUND	SUMMARY:
Total Protein	6.2-8.5 gm. %	6.6 gm %	Low albumin and A/G ratio and slightly low alpha₂ globulin High gamma globulin.
% of total protein: Albumin	54-70	36.5	
Globulins			
Alpha 1	2-5	5.2	
Alpha 2	7-11	6.2	
Beta	8-14	12.5	
Gamma	9-21	39.6	
A/G ratio	1.1-2.4	0.57	

b Hemochromatosis

The level of gamma globulin may be determined also by the gamma globulin turbidimetric test, a modification of Wolfson and Cohn's test for gamma globulin, precipitation with 22 per cent sodium sulfate followed by micro-Kjeldahl distillation, photometric microdetermination, zinc sulfate turbidity test, and determination of I^{131} gamma globulin [146 147,155 174,255 330 331,333 480 509 524 527 569] Eisenmenger has found higher plasma levels of gamma globulin

PAPER ELECTROPHORETIC ANALYSIS OF SERUM



	COMPONENT	Adult Normals	FOUND	SUMMARY:
	Total Protein	6.2-8.5 gms %	6.7 gms %	Low albumin, slightly increased beta and gamma globulins, therefore low A/G ratio.
% of total protein	Albumin	54-70	45.4	
	Globulins			
	Alpha 1	2-5	4.4	
	Alpha 2	7-11	8.3	
	Beta	8-14	18.7	
	Gamma	9-21	23.2	
	A/G ratio	1.1-2.4	0.83	

c Malnutritional (alcoholic) portal cirrhosis complicated by marked hypersplenism

PAPER ELECTROPHORETIC ANALYSIS OF SERUM



	COMPONENT	Adult Normals	FOUND	SUMMARY
	Total Protein	6.2-8.5 gms.%	6.5 gms.%	Low Albumin and A/G ratio. High Alpha 1, Alpha 2 and Beta Globulins
% of total protein	Albumin	54-70	42.4	
	Globulins			
	Alpha 1	2-5	6.6	
	Alpha 2	7-11	13.0	
	Beta	8-14	21.1	
	Gamma	9-21	16.9	
	A/G ratio	1.1-2.4	0.74	

d Secondary biliary cirrhosis due to adenocarcinoma of pancreas, symptoms present for two and one-fourth years

as determined electrophorectically in patients with cirrhosis without ascites (mean value, 3.70 gm./100 cc. plasma) than those with ascites (mean value 2.25 gm./100 cc. of plasma).[174] Inasmuch as the osmotic effect of gamma globulin is half that of albumin it is understandable why cirrhotics with very low plasma levels of albumin and high levels of plasma gamma globulin retain fluid. While hepatitis may be associated with increased levels of plasma

PAPER ELECTROPHORETIC ANALYSIS OF SERUM



COMPONENT	Adult Normals	FOUND
Total Protein	6.2–8.5 gm %	5.7 gm %
% of total protein: Albumin	54–70	43.3
Globulins		
Alpha 1	2–5	6.7
Alpha 2	7–11	13.5
Beta	8–14	15.4
Gamma	9–21	21.1
A/G ratio	1.1–2.4	0.76

SUMMARY: Globulins all slightly high, albumin low.

f Same case as 2d nine months later

PAPER ELECTROPHORETIC ANALYSIS OF SERUM



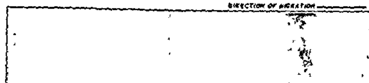
COMPONENT	Adult Normals	FOUND
Total Protein	6.2–8.5 gm %	11.6 gm %
% of total protein: Albumin	54–70	17.0
Globulins		
Alpha 1	2–5	2.4
Alpha 2	7–11	3.3
Beta	8–14	7.1
Gamma	9–21	70.2
A/G ratio	1.1–2.4	0.2

SUMMARY:

g Postnecrotic cirrhosis, female, age twenty-one, sequella considered to be infectious hepatitis

gamma globulin, persistent increases indicate transition to cirrhosis or chronic hepatitis [659] Hypergammaglobulinemia is also seen in lymphoma, sarcoidosis, lymphopathia venereum, rheumatoid arthritis, multiple myeloma, lupus erythematosus, tuberculosis, leukemia and various chronic infectious diseases. Slowly decreasing levels of plasma gamma globulin in patients with established cirrhosis may indicate progressive hepatic insufficiency, development of hepatoma, metastatic carcinoma, hepatic amyloidosis and relief of

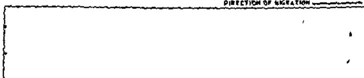
PAPER ELECTROPHORETIC ANALYSIS OF SERUM



COMPONENT		Adult Normals	FOUND	SUMMARY:
Total Protein		6.2–8.5 gms. %	6.1 gms.%	Slightly low albumin and A/G ratio. Both beta and gamma globulins at upper edge of normal.
% of total protein	Albumin	54–70	50.3	
	Globulins			
	Alpha 1	2–5	4.3	
	Alpha 2	7–11	9.7	
	Beta	8–14	14.3	
	Gamma	9–21	21.6	
A/G ratio		1.1–2.4	1.01	

1 Cholangiolitic hepatitis

PAPER ELECTROPHORETIC ANALYSIS OF SERUM

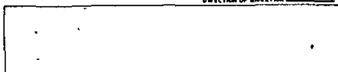


COMPONENT		Adult Normals	FOUND	SUMMARY:
Total Protein		6.2–8.5 gms. %	7.4 gms.%	Low albumin, alpha 1, alpha 2 and beta globulins.
% of total protein	Albumin	54–70	22.9	Very high gamma globulin.
	Globulins			
	Alpha 1	2–5	1.6	
	Alpha 2	7–11	2.7	
	Beta	8–14	4.9	
	Gamma	9–21	67.9	
A/G ratio		1.1–2.4	0.27	

f Postnecrotic cirrhosis, female, age seventeen, clinical features of Cushing's disease

obstruction of the extrahepatic biliary system in cases of secondary biliary cirrhosis or cholestasis

Abnormalities in protein metabolism in patients with cirrhosis are reflected in the flocculation and turbidity tests which, although not specific for hepatic diseases, have widespread use and uniform diagnostic and prognostic value. The results of these tests in various types of cirrhosis may be found in chapters dealing with a specific type of cirrhosis. The *cephalin cholesterol flocculation* test de-



COMPONENT	Adult Normals	FOUND	SUMMARY:
Total Protein	6.2 - 8.5 gms. %	5.7 gms.%	High gamma globulin and low A/G ratio.
% of total protein: Albumin	56-70	37.6	
Globulins			
Alpha 1	2-5	4.6	
Alpha 2	7-11	14.2	
Beta	8-14	14.2	
Gamma	9-21	29.4	
A/G ratio	1.3 - 2.4	0.52	

h Secondary biliary cirrhosis due to adenocarcinoma of pancreas

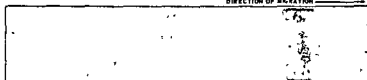


COMPONENT	Adult Normals	FOUND	SUMMARY:
Total Protein	6.2 - 8.5 gms %	6.5 gms %	Low albumin and A/G ratio. All globulins at upper limit. 7% of globulin denatured. Specimen was extremely turbid.
% of total protein: Albumin	56-70	37.3	
Globulins			
Alpha 1	2-5	4.5	
Alpha 2	7-11	12.7	
Beta	8-14	14.6	
Gamma	9-21	22.9	
A/G ratio	1.1 - 2.4	0.60	

j Primary biliary cirrhosis with cutaneous xanthomatosis and increased serum cholesterol and phospholipid

termines qualitative amounts of flocculation of serum upon the addition of a cephalin-cholesterol commercial emulsion Flocculation (normal value 0 to 1+ in forty-eight hours) reflects increased plasma content of albumin and alpha globulin, daylight, heat and ultraviolet light [79 257 272 295 304-370 414 424 559 650] The reduction of alpha globulin in patients with hepatitis or any hepatocellular damage makes this hepatic flocculation very sensitive The test is

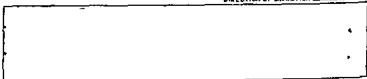
PAPER ELECTROPHORETIC ANALYSIS OF SERUM



	COMPONENT	Adult Normals	FOUND	SUMMARY:
	Total Protein	6.2–8.5 gms %	8.1 gms.%	Slightly low albumin and A/G ratio. Both beta and gamma globulins at upper edge of normal.
% of total protein	Albumin	54–70	50.3	
	Globulins			
	Alpha 1	2–5	4.3	
	Alpha 2	7–11	9.7	
	Beta	8–14	14.1	
	Gamma	9–21	21.4	
	A/G ratio	1.1–2.4	1.01	

1 Cholangiolitic hepatitis

PAPER ELECTROPHORETIC ANALYSIS OF SERUM



	COMPONENT	Adult Normals	FOUND	SUMMARY: Low albumin, alpha 1, alpha 2 and beta globulins. Very high gamma globulin.
	Total Protein	6.2–8.5 gms. %	7.4 gms.%	
% of total protein	Albumin	54–70	22.9	
	Globulins			
	Alpha 1	2–5	1.6	
	Alpha 2	7–11	2.7	
	Beta	8–14	4.9	
	Gamma	9–21	67.9	
	A/G ratio	1.1–2.4	0.29	

f Postnecrotic cirrhosis, female, age seventeen, clinical features of Cushing's disease

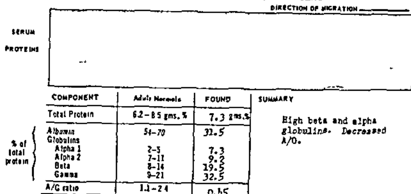
obstruction of the extrahepatic biliary system in cases of secondary biliary cirrhosis or cholestasis

Abnormalities in protein metabolism in patients with cirrhosis are reflected in the flocculation and turbidity tests which, although not specific for hepatic diseases, have widespread use and uniform diagnostic and prognostic value. The results of these tests in various types of cirrhosis may be found in chapters dealing with a specific type of cirrhosis The cephalin-cholesterol flocculation test de-

time in chronic hepatitis and postnecrotic or posthepatitic portal cirrhosis and it is less profoundly increased in fatty or nutritional portal cirrhosis In hemochromatosis, the thymol turbidity is normal initially, and, in biliary cirrhosis the turbidity is elevated in the advanced stage. The thymol turbidity test may be abnormal in a number of extrahepatic diseases already alluded to and is a sensitive test in indicating and following, in particular, the course of posthepatitic or postnecrotic cirrhosis Interpreting the flocculation of the thymol turbidity after twenty-four hours constitutes the thymol flocculation test [340, 368, 370, 432, 533] While not necessarily correlating with the thymol turbidity, it may be especially informative in patients with chronic hepatitis

The zinc sulfate turbidity test already referred to correlates reasonably well with the plasma gamma globulin This test employs a reagent containing zinc sulfate, sodium barbital and barbital [330] Turbidity depends upon the concentration of gamma globulin and lipids in the serum It is one of the most reliable tests indicating cirrhosis and is helpful in following the progressive course of hepatitis into cirrhosis, and in differentiation of cases of hepatocellular from obstructive jaundice [146, 147, 203, 330, 333, 370, 352, 477, 530] A copper acetate turbidity test has been recommended because it is technically simple to perform [530]

Fibrinogen is another globulin of hepatic origin The concentration of plasma fibrinogen has been employed as a hepatic function test in patients with hepatic disease Subnormal levels are usually demonstrated in cases with hepatocellular jaundice or cirrhosis and normal or elevated levels in patients with obstructive jaundice [237, 357, 570] The Factor V concentration factor in the plasma, on the other hand, is decreased in hepatocellular jaundice and is normal or elevated in obstructive jaundice [131a, 139] Other less well known tests indicative of altered metabolism of protein in cases of cirrhosis are the colloidal gold, colloidal red and Takata-Ara tests [234, 368, 367, 372, 373] They are not as uniformly popular as the preceding flocculation or turbidity tests because of expense, decreased hepatic specificity and sensitivity The amino acid tolerance test, employing 10 per cent casein hydrochloride, methionine tolerance test and determination of plasma fibrinogen and urinary and serum amino



PAPER ELECTROPHORETIC ANALYSIS OF SERUM

COMPONENT		Adult Normals	FOUND	SUMMARY
	Total Protein	6.2–8.5 gms. %	7.3 gms.%	High beta and alpha globulins. Decreased A/G.
% of total protein	Albumin	54–70	32.5	
	Globulins			
	Alpha 1	2–5	7.3	
	Alpha 2	7–11	9.2	
	Beta	8–14	19.5	
	Gamma	9–21	32.5	
	A/G ratio	1.1–2.4	0.65	

k Malnutritional (alcoholic) portal cirrhosis, with impending hepatic coma and ascites

positive in nearly 90 per cent of cases of hepatitis and from 50 to 80 per cent of cases of cirrhosis depending upon the extent of hepatocellular degeneration In advanced active or treated portal cirrhosis, primary or secondary biliary cirrhosis and hemochromatosis, the results of the cephalin-cholesterol flocculation tests is abnormal in from 40 to 70 per cent. In these conditions, the tests may also be normal depending upon the extent of hepatocellular damage It is, therefore, a good test in distinguishing cases of hepatocellular from *intrahepatic or extrahepatic jaundice. The test may* also be positive in those diseases associated with hypergammaglobulinemia, malaria, infectious mononucleosis, and diseases of the gastrointestinal tract as chronic ulcerative colitis, regional enteritis and neoplasms

The thymol turbidity test is another excellent test useful in the biochemical detection of cirrhosis Turbidity of the serum depends upon the addition of a barbital and thymol buffer and the presence of increased amounts, particularly, of gamma globulin, beta globulin and serum lipids Similar to the cephalin-cholesterol flocculation test, there are decreased amounts of serum albumin in patients with hepatic disease.[121,261,275,276,292,332-335,350,365,367,368,378,471,477,500,552,582,643,650] *The thymol turbidity test reflects elevation of the serum* gamma globulin and serum lipids more than the cephalin-cholesterol flocculation test, it is more positive over a longer period of

acids are other biochemical tests employed less frequently as hepatic function tests in cases of cirrhosis [18,151,154,178,179,214,314,316,337,349,371,377,358,360,374,423,574,590,633,666,690] These tests have been employed more often experimentally as they offer slight diagnostic benefit and fail to provide uniform results Abnormalities of these tests are due to impaired hepatocellular function in which case amino acids are not deaminated nor synthesized into proteins. Elevation of the blood urea and nonprotein nitrogen in cirrhosis is indicative of renal insufficiency, absorption of nitrogenous substances from the gut and increased catabolism of proteins. In hepatic insufficiency particularly when hepatic necrosis is severe, the blood urea may be low due to impaired deamination Finally, mention should be made of the determination of serum mucoprotein, glycoprotein complexes, as an aid in differentiating cases of hepatocellular jaundice from obstructive jaundice [239-241,676,677] The serum mucoprotein is elevated in obstructive jaundice and hepatic neoplasms, and generally low in cases of hepatitis and cirrhosis This newer hepatic function test is elevated in patients with primary or secondary biliary cirrhosis and low in patients with postnecrotic cirrhosis. The test is a reliable hepatic function test in cases of jaundice Greenspan and Dreiling have studied fractionated globulins as an aid in distinguishing hepatocellular from obstructive jaundice The serum mucoprotein was decreased, the acid precipitable globulin turbidity decreased, and the zinc sulfate turbidity increased in hepatocellular jaundice In obstructive jaundice, the serum mucoprotein was normal or increased, the acid precipitable globulin turbidity increased, and the zinc sulfate turbidity normal or decreased [279]

Decreased serum prothrombin or increase in the prothrombin time is indicative of hepatocellular insufficiency which is commonly observed in cirrhosis The determination of prothrombin time is necessary before performing a needle biopsy of the liver or a surgical operation and as a hepatic function test in cases of liver disease The amount of prothrombin may be measured by a one stage or two stage technique or in response to a small test dose of vitamin K administered hypodermically.[68,356,377,483-487,549,610,611,636] The prothrombin time and its response to parenteral vitamin K is uniformly low in most cases of active cirrhosis, with the exception of those

cases of primary and secondary biliary cirrhosis where hepatocellular dysfunction is minimal The vitamin K tolerance test is important in differentiating cases of obstructive from hepatocellular jaundice inasmuch as bile is necessary before vitamin K can be absorbed from the intestinal tract With the increased administration of broad spectrum antibiotics currently employed, the synthesis of vitamin K may be reduced by sterilization of the large intestine

Carbohydrate Metabolism

The liver maintains an important role in regulating glucose metabolism through which the main supply of energy for the body is derived This organ metabolizes by phosphorylation monosaccharides absorbed from the intestine to glycogen, a process which is known as glycogenesis In addition, some amino acids, fat, pentoses and lactic acid are transformed by the liver to glucose, gluconeogenesis, and then to glycogen The breakdown of glycogen, glycogenolysis, to glucose occurs under hormonal and enzymatic regulation, and, as a result, homeostasis between mobile glycogen stores in the liver and glucose in the blood is present No attempt will be made to review the role of the liver in normal carbohydrate metabolism and the reader is referred to well known classic monographs and textbooks dealing with this rather complex subject (Fig 3) [59-62] [125 149 176 281 276 471 577-591 619 661] As a consequence of hepatic damage, the metabolism of glucose is disturbed and can be recognized fundamentally in different ways

Experimental hepatectomy results in a significant hypoglycemia, a finding that is found uncommonly in severe hepatic damage in humans [illegible] Glucose has been found to be beneficial temporarily in these conditions In the human with hepatic insufficiency, hypoglycemia is prevented by gluconeogenesis from protein fats and pentose sugars Patients with hepatic insufficiency, disturbed glycogenesis and glycogenolysis, manifest themselves, furthermore, in abnormal glucose-tolerance tests not unl[illegible] sults observed in diabetes mell[illegible] cem[illegible] te[illegible] (hyperglycemia), in-

ducts by the liver. Bile salts are synthesized in the liver from cholesterol, and, in addition, the liver metabolizes other steroids, such as, estrogen, testosterone, progesterone and the corticoids.

Hepatic insufficiency or obstruction of the intrahepatic or extrahepatic bile ducts are reflected in altered lipid metabolism and are recognized by various physical and biochemical findings In patients with obstructive lesions of the intrahepatic or extrahepatic bile ducts, xanthomatosis may occur dependent upon marked elevations of the serum cholesterol and phospholipids On the other hand, hepatic insufficiency occurring in cirrhosis may reflect itself in reduced plasma cholesterol esters and in severe hepatocellular necrosis. In addition, reduction in the phospholipids, and low levels of plasma cholesterol esters in hepatic disease, are evidence of marked hepatocellular dysfunction or malnutrition and may be of value with the conventional hepatic function tests in distinguishing hepatocellular from obstructive jaundice.[190-192 234-235 264 295 296 307 471 472 474 476 479 535 592 602 603 639 641] On the other hand, some investigators have found that low cholesterol esters in the presence of normal results of hepatic function tests suggest biliary obstruction.[307 479] In general it has been noted that increased amounts of plasma cholesterol, cholesterol esters and phospholipids are found in biliary cirrhosis, whereas normal amounts occur in most types of cirrhosis. Some exceptions are cases of postnecrotic cirrhosis and portal cirrhosis in terminal hepatic insufficiency in which case these lipid fractions, particularly the cholesterol esters, are low.

Enyzme Metabolism

The various biochemical activities of the liver including the metabolism of protein, fat and carbohydrates are regulated by a great number of enyzmes and coenzymes, about which very little is known. Cytochemists have divided the enyzmes into four cell fractions, namely, the nucleus, the mitochondria, the microsomes and the soluble components[242 278 549a] The most well-known hepatic enyzmes, abnormalities of which may reflect hepatic insufficiency, are alkaline phosphatase, cholinesterase, glutamic oxalacetic transaminase and glutamic pyruvic transaminase.

The liver has been recognized as one of the sources which synthesize and excrete alkaline phosphatase into the biliary system

sulin tolerance, galactose tolerance, and levulose tolerance. There are also elevations in the pyruvic acid in the blood.[7-9,27,312,344,345,384,394,400,422,436,440,471,472,474,496,558,560,574,578,629,662] Abnormalities in these tests, which are based on the role of the liver in the metabolism of carbohydrates, occur more frequently in patients with cirrhosis than viral hepatitis, and, as a result, these cases are often labeled as having "hepatogenic diabetes."

The impaired transformation of galactose to glucose by the liver in hepatic insufficiency is the basis of the galactose tolerance test, but, for all practical purposes, this test as a hepatic function test is unreliable and less specific than the more conventional ones employed. The determinations of fasting blood lactic acid or pyruvic acid, inconsistently elevated in hepatic insufficiency, are not reliable or sensitive hepatic function tests.[11,440]

Fat Metabolism

The liver plays an important role in the metabolism of lipids in several ways. Bile acids excreted by the liver emulsify undigested fat. Pancreatic and intestinal lipases, break fat down into fatty acids, glycerol and various glycerides, preparatory to their absorption into the intestinal lymphatics system and the portal venous system. In the liver, fatty acids absorbed from the intestine or obtained from carbohydrates, proteins or other metabolites are synthesized and oxidized enzymatically with acetyl C. A.[8,107,260,280,602]

Desaturating the fatty acids occurs by altering the length of the carbon chain, and ketone bodies are produced. The liver also mobilizes depot fat and, in certain conditions such as diabetes mellitus, Cushing's syndrome, obesity, starvation or exposure to hepatotoxins, this organ's normal content of 2 to 4 per cent of fat may be increased to very large amounts resulting in impaired hepatic function.[169,345,687a] Phospholipids, which are mainly synthesized in the liver from fatty acids, glycerol, phosphate and choline, inositol and ethanolamine, aid, presumably because of their solubility, in the absorption and transport of fat. The liver also plays an important role in the metabolism of cholesterol. This sterol is absorbed from exogenous sources and is also synthesized in the body, principally in the form of esters which are degraded and excreted into the bile

necrosis and are useful when employed serially in following the clinical course of these patients.[23 115 125 407,409 418 807 652-653] In fact, these tests and the serum cholinesterase have been of inestimable value in following the clinical course of acute hepatitis and active cirrhosis, particularly of the postnecrotic variety (Table XIII).

Vitamins

The liver plays an important role in the metabolism and storage of vitamins. Hepatic insufficiency may reflect itself in disturbed utilization or deficiency of these substances. The production of experimental nutritional hepatic disease, the role of vitamins B and E and abnormalities in the metabolism of the fat-soluble vitamins in experimental biliary obstruction have been alluded to in previous chapters

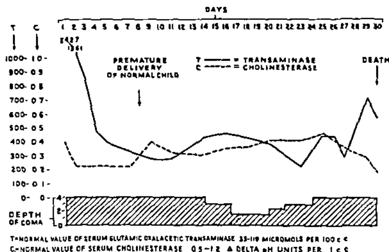


Fig 4 Results of serial determinations of serum transaminase (SGO T) and serum cholinesterase of a patient with early posthepatitic, postnecrotic cirrhosis in hepatic coma Treatment consisted of conventional therapy and massive doses of a corticosteroid agent, sodium glutamate, broad spectrum antibiotic, cleansing enemas and dietary feedings high in calories, but without protein The premature infant did not have icteric viral hepatitis, and "compensatory hepatosplenomegaly." Jaundice disappeared shortly after birth

Determination of the serum alkaline phosphatase is employed as a hepatic function test and abnormalities in the activity of this enzyme are attributed to increased production within the liver and impaired biliary excretion.[83,84,95,96,207,208,434] The serum alkaline phosphatase may be markedly increased in patients with intrahepatic or extrahepatic obstruction of the biliary system excluding congenital biliary atresia, minimally to markedly increased in parenchymal hepatic damage, such as, hepatitis, neoplasms, infiltrative or granulomatous diseases, and normal in inactive portal cirrhosis In addition, when the serum alkaline phosphatase is elevated in the absence of other abnormal hepatic function tests or skeletal diseases, one should suspect granulomatous disease of the liver, obstruction of the biliary system, collagen disease, hemochromatosis and metastatic neoplasms of the liver.[119,136,223,247,248,401,530,661,662] Slowly, progressive elevation of this enzyme should suggest primary or secondary neoplastic involvement of the liver or biliary system.

The serum cholinesterase has become a popular hepatic function test This enzyme apparently is formed by the liver and reflects hepatocellular activity In patients with hepatic insufficiency due to hepatitis, cirrhosis, neoplasm or obstructive lesions of the biliary tract, the serum cholinesterase activity may be reduced[5,14,145,342,379,349,405,625,626,665,671] The test is not specific for any type of hepatic disease and may be useless in differentiating hepatocellular from obstructive jaundice Its most significant use appears to be serial determinations, which afford information pertaining to the course and prognosis in patients with parenchymal hepatic damage (Fig 4) Among the newer tests which also reflect the integrity of the hepatic cells in patients with liver diseases are the serum glutamic oxalacetic transaminase (SGO-T) and the serum glutamic pyruvic transaminase (SGP-T). Transaminase is a specific enzyme concerned with the transfer of alpha-amino nitrogen of aspartic acid to alpha-ketoglutaric acid The result of this synthesis is a new amino acid, glutamic acid and a new alpha-keto acid, oxaloacetic acid.[160,243,340,341,692-695] These enzymes appear to be highly specific for patients especially with hepatic insufficiency and myocardial infarction. Marked elevations are found in patients with hepatitis, cirrhosis and other hepatic lesions depending upon hepatocellular

scurvy unless prolonged malnutrition is accompanied by deficient dietary intake of this vitamin. Low plasma levels of ascorbic acid may be determined in these instances. Ascorbic acid has been demonstrated to enhance the intestinal absorption of iron, but its role in iron metabolism requires further clarification.[122,245]

Most of the vitamins of the B complex group are stored in the liver and play an important role in intermediary metabolism. In association with protein-deficient diets, deficiency of vitamin B complex enhances fatty infiltration of the liver and its transition into cirrhosis. Deficiency of vitamin B_1 or thiamine may occur in portal cirrhosis in alcoholics in the form of polyneuritis of beriberi, Wernicke's hemorrhagic polioencephalitis and fatty infiltration of the liver. It is not known definitely whether a deficiency of riboflavin or vitamin B_2 plays a role in patients with liver disease or hepatic insufficiency Pellagra due to a dietary deficiency of niacin or vitamin B_8 is infrequently observed in patients with nutritional portal cirrhosis who subsist on diets low in protein Other than being associated with the experimental production of fatty infiltration of the liver, little is known about the significance in hepatic diseases in humans of deficiencies of pyridoxine, pantothenic acid and vitamin B_{12} (extrinsic factor).

Minerals

The liver also plays an important role in the metabolism of various minerals Abnormal distribution of minerals in the liver and blood occurs in various specific hepatic diseases and in patients with hepatic insufficiency

The metabolism of iron in patients with iron-storage diseases, hemochromatosis and hemosiderosis, is discussed in Chapter 10 The absorption of ferric ion in the small intestine is greatly increased in certain conditions such as iron-deficiency anemia, hemochromatosis, malnutrition, pregnancy, and childhood Excessive iron storage is found in the liver and reticuloendothelial system Iron is absorbed and metabolized normally across the intestinal barrier with apoferritin, transported in the blood with a beta globulin, siderophilin, to the liver, where it is stored as ferritin and iron The relationship of excessive absorption, transport and

Vitamin A and carotene depend upon the intestinal mucosa and bile salts for proper absorption into the blood and storage in the liver. The liver regulates the level of vitamin A in the blood. In patients with various types of hepatic disease, impairment of vitamin A metabolism is reflected in low concentrations of this substance in the liver and blood and, occasionally, clinical manifestations of avitaminosis A. The absorption of vitamin A may be impaired in patients with obstructive lesions of the intrahepatic or extrahepatic biliary tree and storage of this vitamin is impaired in cirrhosis and in cases of malnutrition.[74, 253, 415-417, 466, 475, 492, 494, 667, 690] Low amounts of plasma or hepatic vitamin A and carotene also may be determined in patients with obstructive jaundice by a flat oral vitamin A tolerance test and by impaired distribution of vitamin A in the liver determined histologically by fluorescence. Vitamin A deficiency expressed by low plasma and hepatic content of vitamin A and carotene and an abnormal dark adaptation time have also been demonstrated to be present in patients with portal cirrhosis.[253]

Obstruction of the intrahepatic and extrahepatic biliary system leading to reduced amounts of bile salts and the ingredients necessary for the intestinal absorption of vitamin D may induce osteomalacia. This is observed clinically, particularly in patients with primary or secondary biliary cirrhosis, in whom osteomalacia and osteoporosis, manifest themselves in the form of skeletal pain and fractures.[320, 321]

The significance of low plasma concentrations of vitamin E or alpha-tocopherol or their impaired intestinal absorption in patients with various types of liver disease is unknown.[317, 318, 470] Mention has been made already of nutritional hepatic necrosis produced experimentally in animals fed diets deficient in vitamin E. The role of the fat-soluble vitamin K in hepatic insufficiency has been discussed under protein metabolism in this chapter. Deficiency of this vitamin, necessary for the formation of prothrombin, may occur due to impaired absorption from the intestines in patients with obstructive jaundice and in hepatic insufficiency.

The liver apparently plays an insignificant role in the metabolism of vitamin C. Patients with hepatic insufficiency do not exhibit

the absorption of calcium is impaired.[32 320-322] Hepatic disease has been implicated in the malabsorption syndrome.[1-9 203 320 321 427 443 622] The mechanisms involved may be disturbed bile-pigment metabolism and excretion, endocrine disturbances, infections, drugs, alcohol, vitamin B_{12} deficiency, agammaglobulinemia, impaired selectivity and efficiency of intestinal absorption, intestinal motility, and lymphatic circulation (Table III). Along these lines, B[131]-

TABLE III

CLASSIFICATION OF LIVER DISEASES PRODUCING MALABSORPTION SYNDROMES

The following categories of hepatic disease may be associated directly or indirectly with intestinal malabsorption and are grouped according to the principle pathophysiological defect

1 Insufficiency of Bile Salts
   Cholestatic Hepatic Disease
   A Intrahepatic Type
      Cholangiolitic Hepatitis
      Primary Biliary Cirrhosis

   B
      Cholestasis (Cholangitis) due to stone, neoplasm, stricture anomaly parasites chronic inflammation and xanthoma of extrahepatic biliary ducts
      Secondary Biliary Cirrhosis

2

      Neoplasm
      Infiltrations
      Granulomas
      Parasitic Infestations
      Veno Occlusive Disease
      Hypogammaglobulinemia

3 Pancreatic Insufficiency
      Chronic Relapsing Pancreatitis
      Congenital Cystic Fibrosis of the Pancreas
      Kwashiorkor
      Cirrhosis

4 Metabolic and Hepatic Disease
      Diabetes Mellitus
      Hyperthyroidism
      Hepatolenticular Degeneration
      Galactosemia
      Iatrogenic Fatty Liver, (Steroid or Antibiotic Induced)

5 Iron Storage Disease
      Malnutritional Hemosiderosis (Cytosiderosis)
      Hemochromatosis

6

storage of iron in hemochromatosis has been established, although available evidence suggests that excessive deposits of the metal alone do not account for pathologic lesions and altered hepatic function in this disease In this condition, increased serum iron usually coincides with saturation of the iron-binding protein, which is some quarters, is presumptive diagnosis of hemochromatosis. The level of serum iron has been found increased in patients with acute hepatitis, posthepatitic portal cirrhosis, and postnecrotic cirrhosis, and this has been considered as an indication of hepatocellular necrosis It has been demonstrated to be normal or low in patients with other types of cirrhosis and extrahepatic obstruction.[116 162,321 322 384 436,493 502 533] Serial determinations of serum iron in patients with hepatic insufficiency may serve as a valuable therapeutic and prognostic guide Elevation of plasma ferritin may occur in patients with acute necrosis of the liver, viral hepatitis and Hodgkin's disease but apparently is found infrequently in cirrhosis[304] Ferritin has been considered to be identical with VDM and to exert vasodepressive and antidiuretic actions [19,387 488 567]

Copper, considered essential in the metabolism of respiratory enzymes and hemoglobin, is deposited in the liver in excessive amounts in patients with hepatolenticular degeneration and those in whom the dietary intake of this substance is excessive The role of abnormal copper metabolism in hepatolenticular degeneration is discussed in Chapter 11 The metabolism of copper appears undisturbed in cirrhosis[216] A deficiency of magnesium has been reported in patients with cirrhosis, particularly following the administration of ammonium chloride in alcoholics, and in those administered magnesium-free parenteral fluids. A syndrome has been described consisting of muscular tremor, choreiform movements and, occasionally, convulsive seizures[197 198 601] The level of iodine in the serum may be low in patients with cirrhosis but the significance of the finding awaits clarification[338] Serum zinc concentrations have been reported to be low in patients with severe cirrhosis in contradistinction to other hepatic diseases, and the serum level of this metal appears to be related to the severity of the disease.[613 614] Reduction in the level of serum calcium may be found in patients with primary or secondary biliary cirrhosis due to a hepatobiliary steatorrhea and in nutritional portal cirrhosis when

the absorption of calcium is impaired.[12,320-327] Hepatic disease has been implicated in the malabsorption syndrome[139,203,320,321,427,445,627] The mechanisms involved may be disturbed bile pigment metabolism and excretion, endocrine disturbances, infections, drugs, alcohol, vitamin B_{12} deficiency, agammaglobulinemia, impaired selectivity and efficiency of intestinal absorption, intestinal motility, and lymphatic circulation (Table III). Along these lines, I[131].

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1. Insufficiency of Bile Salts
   - Cholestatic Hepatic Disease
     - A. Intrahepatic Type
       - Cholangiolitic Hepatitis
       - Primary Biliary Cirrhosis
       - Acholangitic Biliary Cirrhosis
       - Iatrogenic (Drug) Cholestasis
       - Chronic Intrahepatic Obliterating Cholangitis
     - B. Extrahepatic Type
       - Cholestasis (Cholangitis) due to stone, neoplasm, stricture anomaly, parasites chronic inflammation and xanthoma of extrahepatic biliary ducts
       - Secondary Biliary Cirrhosis
2. [illegible]
   - [illegible]
   - Infiltrations
   - Granulomas
   - Parasitic Infestations
   - Veno Occlusive Disease
   - Hypogammaglobulinemia
3. Pancreatic Insufficiency
   - Chronic Relapsing Pancreatitis
   - Congenital Cystic Fibrosis of the Pancreas
   - Kwashiorkor
   - Cirrhosis
4. Metabolic and Hepatic Disease
   - Diabetes Mellitus
   - Hyperthyroidism
   - Hepatolenticular Degeneration
   - Galactosemia
   - Iatrogenic Fatty Liver, (Steroid or Antibiotic Induced)
5. Iron Storage Disease
   - Malnutritional Hemosiderosis (Cytosiderosis)
   - Hemochromatosis
6. Primary Absorptive Defects of Small and Large Intestines, Hepatic Diseases associated with chronic ulcerative colitis, regional *enteritis*, *coeliac disease*, tropical and nontropical sprue, primary amyloidosis carcinoma, sarcoma, lymphoma, sarcoidosis nonspecific gastro enteritis and *enterocolitis*

labeled triolein and I^{131}-labeled oleic acid have been employed in the study of absorptive conditions in man.[39,40,312] In some instances impaired absorption of I^{131} was found to occur more in obstructive jaundice than in hepatocellular jaundice Hypophosphoremia, hyponatremia, hypokalemia and respiratory alkalosis are found in advanced hepatic insufficiency.[12,512] The reader is referred to Chapter 15 for discussion of electrolyte and fluid imbalances in ascites and edema in cirrhosis and to the discussion of this subject in patients in hepatic coma in subsequent paragraphs.

Metabolism of Adrenal and Sex Hormones

Decreased excretion of 17-ketosteroids, elevation of urinary corticoids, and increase in the lipid content of the adrenal glands in cirrhosis, in general, may indicate suppressed adrenocortical function and impaired hepatic inactivation of these steroids [63 65 82 137 173 193 204 352 437 523 628 670] Impaired metabolism of hormones may produce sodium and water retention and in the abnormal metabolism of protein, fat and carbohydrates in patients with cirrhosis. On the other hand, an unusual syndrome has been observed in young women with an active cirrhosis, usually postnecrotic in type, with clinical features of Cushing's syndrome, marked hepatic insufficiency and markedly elevated excretion of urinary corticoids [36,65,322]

Estrogen and testosterone are not inactivated in cirrhosis, and, consequently, hyperestrogenism results. Following this condition there occurs elevation of urinary estrogens and feminization in the male in the form of gynecomastia, female habitus, testicular atrophy, alopecia, loss of libido, impotency and possibly palmar erythema and spider angioma [35,39 126 157,225,226 301,352,354 463 523] In the female cirrhotic, hyperestrogenism may be reflected by menstrual irregularities, amenorrhea, acne, and changes in the breast The relationship of hyperestrogenism and spider angioma appears questionable [31-32,35 157,202] Finally, hyperestrogenism in patients with cirrhosis is associated with decreased androgen, which may be directly responsible for testicular atrophy, decreased protein anabolism, negative nitrogen balance, and retention of sodium and contributory to decreased excretion of 17-ketosteroids

Specificity, Selection and Correlation of Hepatic Function Tests in the Diagnosis of Cirrhosis

Various suggested combinations of hepatic function tests, the continued search for the utilization of newer hepatic function tests, and the results obtained from needle biopsies of the liver testify to the fact that confusion exists over the specificity of biochemical findings in diseases of the liver and the plurality of hepatic functions. Perhaps no other organ in the body has so many complex and obscure functions as the liver. Very few of the hepatic function tests actually measure the basic functions of the liver. This is in contrast to diseases of the heart, kidney, pancreas and endocrine system in which tests determining the functions of these organs are more specific. Normal individuals and patients with diseases other than hepatic have been determined to have abnormalities in certain hepatic function tests, especially the bromsulfalein, flocculation, turbidity, alkaline phosphatase, cholesterol-cholesterol ester, transaminase, cholinesterase, albumin and globulin determinations. False-negative hepatic function tests may be found commonly during menstruation, pregnancy, advanced age or in patients with diseases of the gallbladder, infections, collagen diseases, rheumatoid arthritis, chronic ulcerative colitis, regional enteritis, sprue, malnutrition, obesity, alcoholism, hyperthyroidism, diabetes mellitus, shock, nephrosis, glomerulonephritis and many others. For this reason the proper selection of hepatic function tests employed in the diagnosis of diseases of the liver is important, and, similarly, whenever possible the physician should interpret the results of these biochemical tests in the light of a histological diagnosis of a hepatic specimen obtained, preferably by needle biopsy.

In order to select a proper hepatic function test in the diagnosis of any hepatic disease, one should rely on a battery of hepatic tests or a liver profile.[230, 277, 363, 386, 439, 471, 472, 476, 478, 601, 641, 649, 680, 691] Zieve and Hill in 1955 found that the bromsulfalein dye retention was the most reliable hepatic function test in the detection of cirrhosis.[689] They also demonstrated that this test and the zinc sulfate turbidity, hippuric acid test, and quantitative determination of urinary coproporphyrin contributed independently to the discrimination be-

labeled triolein and I^{131}-labeled oleic acid have been employed in the study of absorptive conditions in man[39,40,312] In some instances impaired absorption of I^{131} was found to occur more in obstructive jaundice than in hepatocellular jaundice. Hypophosphoremia, hyponatremia, hypokalemia and respiratory alkalosis are found in advanced hepatic insufficiency.[12,512] The reader is referred to Chapter 15 for discussion of electrolyte and fluid imbalances in ascites and edema in cirrhosis and to the discussion of this subject in patients in hepatic coma in subsequent paragraphs

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11	Bile duct stricture	13.3/27.0	31.6	0	1.5	2.8	10	3.9/3.7	23	10	135	35	—	Hepatic insufficiency
12	Cholangiolitic hepatitis secondary	12.1/21.2	18.2	0	21.2	13.4	61	3.1/3.3	8.4	109	100	1.28	—	None
13	Biliary cirrhosis	7.0/12.1	8.2	11	17.5	21.8	50	2.1/1.6	19.4	81	51	27	—	Adenocarcinoma pancreas
14	Secondary biliary cirrhosis	9.1/11.5	22.4	2+	11.8	13.3	73	2.1/1.0	21.2	178	176	1.76	—	Stricture bile duct
15	Metastatic adenocarcinoma liver	12.0/21.3	28.7	2+	7.6	10.5	41	3.3/2.6	35.5	150	58	30	—	Xanthomatosis
16	Fatty liver and Diabetes mellitus	11/64	—	0	7.8	2.6	100	3.4/2.2	11.4	118	72	85	0	Hepatomegaly
17	Hepatolenticular degeneration	1/1.0	0	2+	5.5	5.7	16	3.6/3.4	10	65	210	58	6	None
18	Hemochromatosis	0.1/0.9	2.5	0	12.2	1.2	100	4.2/3.8	9.5	212	152	95	5	None
19	Portal cirrhosis to hepatic coma	21.7/12.2	—	2+	8.9	7.4	51	3.0/3.2	31.5	182	121	0.23	—	Stricture bile duct
20	Hepatic coma and death	21.0/19.5	31	0	2.0	7.0	52	3.8/1.1	18.4	212	5000+	0.10	—	Metastatic hepatic disease (?)
	7 days later	21.8/58.0	—	1+	2.2	8.2	33	—		—	646	0.07	—	—
21	Hepatic coma survival	2.0/5.5	—	2+	17.9	16.0	56	3.0/2.9	10.2	72	132	0.56	—	Portal cirrhosis (?)
	1 mo. later	0.57/1.09	—	2+	5.5	11.2	73	3.1/2.1	11.4	110	318	0.4	37	None
22	Infectious hepatitis	6.2/9.4	6.4	51	12.4	11.7	52	3.2/2.9	10.8	218	609	0.64	—	None
	3 weeks later	8.4/2.1	14	21	10.2	10.4	67	3.3/2.6	11.2	174	299	0.90	18	None

TABLE IV
RESULTS OF BLOOD HEPATIC FUNCTION TESTS IN VARIOUS TYPES OF DISEASES OF THE LIVER

	Diagnosis	*Bilirubin*	*Alk Phosphatase*	*CCF 48 hrs*	*$ZnSO_4$ Turbidity*	*Thymol Turbidity*	*Prothrombin Time*	*A/G*	*Mucoprotein*	*Iron*	*Transaminase (SGOT)*	*Cholinesterase*	*BSP*	*Complication*
	Normal Values	0.2 D / 1.0 I	1.5-10	0,1+	3.5-10.5	0-7	100%	3.5 / 2.5	10-13	70-185	33-119	0.5-1.2	0.5%	
1	Portal cirrhosis	.5 / 4.5	2.4	3+	12.7	8	57	3.0 / 4.5	13.5	83	177	44	—	Esophageal hemorrha[illegible]
	After P C shunt	1.1 / 3.5	4.9	2+	21.5	11.9	44	3.0 / 3.6	32	193	20	35	—	Ascites
2	Portal cirrhosis	20 / 73	3.8	3+	7.3	6.3	56	3.0 / 3.9	8.7	172	—	—	—	Abdominal pain
3	Portal cirrhosis	08 / 1.1	1.6	2+	15.4	8.7	100	3.2 / 3.2	10.6	127	245	83	12	Latent
4	Portal cirrhosis	5.8 / 16.8	8.9	1+	22.6	11.7	35	3.3 / 3.6	—	—	355	.25	—	Chlorpromazine hepa[illegible]
5.	Portal cirrhosis	0.2 / 1.0	—	1+	5.2	4.0	44	3.9 / 3.0	—	—	132	60	24	Delerium tremens
6	Portal cirrhosis	2.6 / 5.5	6.4	3+	4.7	12.4	35	3.0 / 3.8	6.5	165	225	.26	38	Brucellosis
7	Postnecrotic cirrhosis	13 / 20	—	0	25.1	2.4	100	3.4 / 2.9	12.8	121	173	46	6	Esophageal hemorrha[illegible]
	After S R shunt	79 / 2.5	—	0	23.0	0.9	67	2.9 / 2.9	29.5	143	218	.25	11	None
8.	Postnecrotic cirrhosis	0.4 / 1.6	3.3	3+	21.9	23.1	64	2.8 / 3.9	5.5	193	348	30	18	None
9	Postnecrotic cirrhosis	1.5 / 3.2	1.5	3+	18.3	22.4	73	3.3 / 4.0	7.0	185	201	35	46	None
10	Primary biliary cirrhosis	4.2 / 8.6	20.9	2+	15.2	11.7	67	3.2 / 4.6	15.3	162	237	.50	—	Xanthomatosis
11	Bile duct [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
12	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

2. Zinc sulfate turbidity.
3. Serum cholinesterase or serum transaminase.
4. Serum albumin and globulin.
5. Prothrombin time
6. Direct and indirect serum bilirubin.
7. Serum cholesterol and cholesterol esters
8. Cephalin-cholesterol flocculation.
9. Thymol turbidity.

The increased use of needle biopsy of the liver has demonstrated that there is a better correlation between hepatic function tests with histopathological alterations in the diseased liver obtained by needle biopsy than at necropsy [203,213,466,472,478,558,823,839,841,847] Hepatic necrosis correlates reasonably well with abnormalities in the bromsulfalein, serum transaminase, serum cholinesterase, cephalin-cholesterol flocculation, thymol turbidity, and serum albumin and globulin determinations Cirrhosis coincides well with alterations in the thymol turbidity, cephalin-cholesterol flocculation, zinc sulfate turbidity, gamma globulin turbidity, serum albumin and globulin, and elevation of the erythrocyte sedimentation rate. The degree of morphological hepatic damage has been noted by some observers to be correlated statistically with the degree of abnormality of these various tests [467,472,478] In cirrhosis, in general, this quantitative correlation is significant in abnormalities in the flocculation and turbidity determinations, the direct serum bilirubin, and the serum albumin and globulin. Elevation of the direct bilirubin, alkaline phosphatase, cholesterol, phospholipids and mucoprotein in the blood are observed in patients with primary and secondary biliary cirrhosis prior to the onset of progressive hepatocellular damage

Pathological Manifestations

The pathological features observed in patients with cirrhosis and hepatic insufficiency have been alluded to in preceding chapters. The liver is characterized by regenerative nodules, fibrosis and, occasionally, fatty infiltration, hepatocellular necrosis and deposition of pigments The spleen may become enlarged, fibrotic and congested, disclose chronic perisplenitis and is intimately associated with additional manifestations of portal hypertension such as col-

tween normal and cirrhotic patients In general, these tests have been subdivided into groups reflecting acute or chronic parenchymal damage, and hepatocellular or obstructive jaundice. The importance of selecting a profile of hepatic function tests, for example, is demonstrated in the differential diagnosis of cirrhosis (Table IV). The tests most indicative of acute hepatocellular damage are the direct serum bilirubin, bromsulfalein, cephalin-cholesterol flocculation, serum alkaline phosphatase, serum transaminase, serum cholinesterase, hippuric acid synthesis, two-hour quantitative urine urobilinogen and the cholesterol esters In addition, the prothrombin time, serum albumin, serum globulin, thymol turbidity, zinc sulfate turbidity and gamma globulin turbidity determinations are more commonly abnormal in patients with chronic hepatocellular insufficiency. In advanced cirrhosis, the cholesterol esters, blood ammonia, urinary amino acids, serum transaminase, serum iron, and serum cholinesterase are the most sensitive hepatic function tests There are really no reliable tests to differentiate primary from secondary biliary cirrhosis, and, of course, in most hands, needle biopsy of the liver adds little if any confirmative diagnostic information One should rely then on diagnostic physical findings, the alkaline phosphatase, serum mucoprotein, operative cholangiogram, and surgical exploration of the common bile duct It has been noted that a slow progressive elevation of the serum alkaline phosphatase and serum mucoprotein are more suggestive of extrahepatic than intrahepatic biliary obstruction, particularly in patients with neoplastic obstructive jaundice. In some patients with secondary biliary cirrhosis due to parasitic, calculous, or stenotic lesions of the extrahepatic biliary system, the fluctuant or persistent elevations of the direct serum bilirubin, serum alkaline phosphatase and serum mucoprotein should suggest this condition In hemochromatosis it is recognized that the hepatic function tests can be normal or only slightly altered In these cases the determination of the serum iron and saturation of the iron-binding globulin may offer presumptive evidence of this condition.

The following profile of hepatic function tests offers practical diagnostic information on cirrhosis:

1. Bromsulfathalein retention.

TABLE V

CLINICAL COURSE AND LABORATORY DATA OF A 28 YEAR MALE WITH POSTNECROTIC CIRRHOSIS, ASCITES, PLEURAL AND PERICARDIAL EFFUSION

Clinical Manifestations	*Date* 9 1 53	12 15-54	12 23-54	12 27 55	2 4 55
Body weight lb	168	154	152	140	142
Emaciation	0	+	+	+	+
Jaundice	0	+	+	+	+
Chest pain	0	+	+	−	+
Dyspnea	+	+	+	+	+
Fever	+	101°	102°	99°	102°
Diaphoresis	0	+	+	0	+
Ascites	+	+	+	+	+
Edema	+	+	+	+	+
Pleural effusion	0	+	+	0	+
Pericardial effusion	0	+	+	0	+
Abdominal pain	+	+	+	0	+
Laboratory Data					
Bilirubin serum D/T, mg/100 cc		1.2/3.8	2.7/1.2	−	6.4/10.2
Cephalin flocculation	−	3+	3+	3+	3+
Thymol turbidity, units	−	15.7	15.2	−	14.4
Zinc sulfate turbidity, units	−	−	23.2	−	22.8
Albumin serum, gm/100 cc.	−	1.5	3.7	1.9	2.1
Globulin serum gm/100 cc	−	5.0	5.8	3.2	5.8
Sedimentation rate (Westergren)	−	77	−	15	19
Hemoglobin blood gm/100 cc	−	10.1	−	8.8	10.2
RBC x 10⁶ per cu mm	−	319	−	329	−
WBC per cu mm	−	9750	−	25200	11900
Platelets per cu mm	−	228,000	−	−	256,000
False positive serology	−	+	−	−	+
Hepatomegaly	4f	4f	4f	4f	4f
Splenomegaly	3f	3f	3f	3f	3f
Prothrombin time %	−	55	55	55	
Clinical Course	Dyspnea Asthenia	Same	Same	Same	Hepatic Coma
Treatment	Bedrest 1.0 gm sodium	Vitamins diuretics cortisone high protein high caloric diet pleural, pericardial and abdominal paracenteses, blood transfusions			

melanosis, spider angioma, palmar erythema, telangiectasia, clubbed fingers, white, flat or curved fingernails Important clinical features of hepatic insufficiency in patients with cirrhosis, fever, fetor hepaticus, pruritus, anemia and pre-hepatic and hepatic coma, will be discussed in the succeeding paragraphs

Fever is a common clinical finding observed in patients with cirrhosis indicative of hepatic insufficiency It may be low-grade and associated with a leukocytosis in alcoholics with portal cirrhosis or

lateral portal venous system. The gastrointestinal tract may become congested and edematous The kidneys may disclose congestion, glomerulonephritis or "cholemic" or *bile nephrosis*

Terminal renal insufficiency observed in patients with hepatic diseases has been called the hepatorenal syndrome and may result from hemorrhagic shock, anoxia, *bile nephrosis, fever, intoxication* from drugs, such as sulfonamides, mercurials, carbon tetrachloride or phosphorus, anesthesia, surgical operation, transfusions of blood or thyrotoxicosis [66,90,100 219,268,290,304,359,412,606,633] The pancreas may be congested, inflamed, fibrotic, and contain calculi [315,590] Atrophy of germinal epithelium of the testes, thickening of the lamina propria of the seminiferous tubules, metaplasia of the epithelium of the prostate, and, in males, hyperplasia of the mammary glands are commonly found in patients with advanced cirrhosis [39]

Clinical Manifestations

The symptoms and physical findings of cirrhosis with or progressing to hepatic insufficiency have been referred to in preceding chapters and consist of gastrointestinal features nausea, vomiting, weakness, weight loss, abdominal distention, abdominal pain, diarrhea, steatorrhea, constipation, jaundice, fever, pruritus, hematologic features gastrointestinal bleeding, ecchymosis, petichia, anemia, cutaneous or mucosal bleeding; endocrine features· gynecomastia, loss of hair, amenorrhea, menometrorrhagia, impotence, loss of libido, features of Cushing's disease (Table II) ; *cardiac and* respiratory features dyspnea, chest pain, congestive heart failure, cyanosis, arrhythmias, cough (Table V) ; features of portal hypertension *esophageal varices, hypersplenism, hemorrhoids,* abdominal venous collaterals, Cruveilhier-Baumgarten syndrome, increased cardiac output, fluid and electrolyte imbalance ascites, *edema,* pleural and pericardial effusion, neuropsychiatric features peripheral neuritis, psychoneurosis, psychosis, headache, restlessness, dizziness, sleeplessness, Wernicke's hemorrhagic polioencephalitis, *hepatic coma;* musculoskeletal features muscular wasting, osteomalacia, osteoporosis, muscular rigidity, fractures, emaciation, hernias, urinary features: hematuria, polyuria, oliguria, dysuria; infectious features fever, bronchopneumonia, abscesses; and cutaneous features jaundice, moist deep red tongue,[299] pruritus,

TABLE V

CLINICAL COURSE AND LABORATORY DATA OF A 28 YEAR MALE WITH POSTNECROTIC CIRRHOSIS, ASCITES, PLEURAL AND PERICARDIAL EFFUSION

Clinical Manifestations	*Date* 9 1 53	12 15 54	12 21 54	12 27 55	2 4 55
Body weight, lb	168	154	152	140	152
Emaciation	0	+	+	+	+
Jaundice	0	+	+	+	+
Chest pain	0	+	+	+	+
Dyspnea	+	+	+	+	+
Fever	+	101°	102°	99°	102°
Diaphoresis	0	+	+	0	+
Ascites	+	+	+	+	+
Edema	+	+	+	+	+
Pleural effusion	0	+	+	0	+
Pericardial effusion	0	+	+	0	+
Abdominal pain	+	+	+	0	+
Laboratory Data					
Bilirubin serum D/T mg/100 cc		1 2 / 5 8	2 7 / 12	–	6 1 / 10.2
Cephalin flocculation	–	3+	3+	3+	3+
Thymol turbidity, units	–	15 7	15.2	–	15 4
Zinc sulfate turbidity, units	–	–	25.2	–	22.8
Albumin serum, gm/100 cc	–	1 5	3.8	1 9	2 1
Globulin serum, gm/100 cc	–	5 0	3 8	3.2	3 8
Sedimentation rate (Westergren)	–	77	–	13	19
Hemoglobin, blood gm/100 cc	–	10 1	–	8 8	10 2
RBC x 10⁶ per cu mm	–	3 19	–	3.29	–
WBC per cu mm	–	9750	–	25200	14900
Platelets per cu mm	–	228 000	–	–	256 000
False positive serology	–	+	–	–	+
Hepatomegaly	4f	4f	4f	4f	4f
Splenomegaly	3f	3f	3f	3f	3f
Prothrombin time%	–	35	35	33	
Clinical Course	Dyspnea Asthenia	Same	Same	Same	Hepatic Coma
Treatment	Bedrest 1 0 gm sodium	Vitamins diuretics, cortisone, high protein high caloric diet pleural pericardial and abdominal paracenteses, blood transfusions			

melanosis, spider angioma, palmar erythema, telangiectasia, clubbed fingers, white, flat or curved fingernails Important clinical features of hepatic insufficiency in patients with cirrhosis, fever, fetor hepaticus pruritus, anemia and pre hepatic and hepatic coma, will be discussed in the succeeding paragraphs

Fever is a common clinical finding observed in patients with cirrhosis indicative of hepatic insufficiency It may be low-grade and associated with a leukocytosis in alcoholics with portal cirrhosis or

in patients with primary biliary cirrhosis Patients with posthepatitic portal cirrhosis or postnecrotic cirrhosis commonly have fever which may be high, intermittent or low grade. Fever (Charcot's intermittent fever) may be a presenting complaint with obstructive jaundice and chills in patients with secondary biliary cirrhosis due to recurrent secondary cholangitis Fever may be indicative of a pyogenic or viral infection in cirrhotics, a feature commonly observed in patients with cirrhosis and hypersplenism. In severe or terminal hepatic insufficiency, fever may be very high, with the temperature ranging from 102 to 105° Fahrenheit This common clinical finding indicates a bad prognosis and probably is a sign of progressive hepatocellular necrosis or impaired metabolism of proteins.

Fetor hepaticus or amino breath constitutes one of the most reliable physical findings of severe hepatic insufficiency in patients with diseases of the liver Peculiarly, it is a frequent but inconsistent feature in advanced hepatic insufficiency and is found more frequently in patients with hepatocellular jaundice than jaundice due to extrahepatic biliary obstruction [210 514] The odor is easily recognized, and is characteristic and well appreciated during postmortem examinations particularly when the liver is transected despite lack of pathological evidence of hepatic disease The substance responsible for fetor hepaticus has been identified in the urine from patients with cirrhosis and also healthy individuals. The chemical properties suggest it may be a weak base, probably a tertiary amine, similar to d-methylpiperidine or mercaptan [85,87, 109,142] The odor had been considered to be hepatic or intestinal in origin and temporary intestinal antisepsis does not decrease the urinary excretion of fetor The physician will find fetor hepaticus, when present, a valuable prognostic physical finding, persistence of which indicates a bad prognosis, whereas waning and cessation may signify recuperation

Pruritus, invariably but not always associated with clinical jaundice, is a frequent symptom of primary and secondary biliary cirrhosis In a case of the former disease, it may be the presenting complaint. Itching is uncommon in other types of cirrhosis except in an occasional patient with postnecrotic cirrhosis, hepatic insuf-

ficiency and hepatocellular jaundice. While pruritus and jaundice usually coexist in patients with both types of biliary cirrhosis, these features are associated, in addition, with dark urine, acholic stools and occasionally steatorrhea. The cause of pruritus in these conditions is unknown, and it has not been proved to be caused by increased cholesterol, alkaline phosphatase, phospholipids, bilirubin or bile salts. The relationship of mucunain, the active pruritogenic proteinase of cowage, to this problem appears obscure but worthy of further study.[553] The occasional ameliorative effects from methyl testosterone, adenosine-5-monophosphate, antihistaminic agents, reserpine, phenobarbital, cortisone or corticotropin offer no positive clue to the pathogenesis of pruritus in biliary cirrhosis. An elevation of histamine in the blood has been demonstrated to be proportional with pruritus in patients with cirrhosis or extrahepatic biliary obstruction.[13, 406]

The various types of anemia associated with cirrhosis have been a subject of interest and controversy. The liver has been recognized to store the erythrocyte maturing factor, play an important role in the metabolism of ferritin, fibrinogen, prothrombin and vitamin B_{12} and to aid in the formation and destruction of erythrocytes. A hypochromic, microcytic or normocytic anemia may be recognized in patients with cirrhosis who have bled from hemorrhagic lesions of the gastrointestinal tract such as esophageal varices, hemorrhagic gastritis and gastric or duodenal ulcers, hemorrhoids or from oozing due to decreased fragility or thrombocytopenia. Bleeding tendency due to uremia which may occur in cirrhosis is best explained by thrombocytopenia.[497] Cirrhosis may be accompanied by hypersplenism as a manifestation of portal hypertension and in this condition, leukopenia, thrombocytopenia, normoblastic hyperplasia of the bone marrow, reticulocytosis, elevation of the indirect serum bilirubin, hemolytic and/or normocytic anemia, hemolytic jaundice, hemosiderosis of the liver and spleen and decreased amounts of fecal and urine urobilinogen are prevalent.[28, 192, 224, 237a, 255, 257, 331b, 317, 635, 810, 643, 846, 655, 675] Decreased erythrocyte-survival time has been demonstrated in patients with portal cirrhosis, which may also explain the increased indirect bilirubin observed frequently in this condition.[8] The association of erythroblastosis

fetalis or sickle-cell anemia with cirrhosis in infants has been alluded to, and it is conceivable that hemolytic anemia in this condition may contribute to the pathogenesis of cirrhosis by anoxia and intrahepatic stasis of bile

A specific anemia, usually macrocytic anemia, has been found frequently in patients with cirrhosis In many instances, cirrhosis *may be complicated by loss of blood*, neoplasms, chronic infection, or malnutrition which in themselves may produce anemia. The incidence of macrocytic anemia in patients with cirrhosis has been found to vary from 2 to 89 per cent [251,290,675] The pathogenesis of this type of anemia, however, is obscure Malnutrition, alcoholism, intestinal malabsorption, decreased storage or utilization of the erythrocyte maturing factor, impaired storage or increased requirement of vitamin B_{12} or folic acid, reticulocytosis, hemolysis and hemodilution have been suggested as etiological factors producing the anemia of cirrhosis [25 41 58,118 228,284 289 290 327,343 536 556 557 617 653 671 675] An increase in the mean diameter of erythrocytes singularly or *associated with anemia has been correlated with the duration and* improvement of hepatic insufficiency [251 343] The macrocytosis of cirrhosis is similar to that observed in patients with pernicious anemia in relapse, but the therapeutic response to vitamin B_{12} or liver extract and the presence of histamine achlorhydria are usually lacking [251 266 287 289 291 343 517 675] The most convincing evidence to explain macrocytosis in patients with cirrhosis appears to be the result of protein malnutrition and hemolysis of erythrocytes, but further confirmatory studies are necessary The level of serum vitamin B_{12} has been reported to be normal, increased, and decreased in patients with cirrhosis [22 287 288 297 488 596] It has been noted that prothrombin, Factor V and Factor VII, are depressed in chronic liver disease, depression of Factor V indicating a poor prognosis.[131a] A normoblastic hyperplasia of the bone marrow occurs most frequently in patients with cirrhosis and anemia. The increased immun*ological potential of patients with chronic liver disease* has been demonstrated by a cirrhotic who produced large amounts of tetanus antitoxin [263] The reader is referred to Chapter 10 for the relationship of chronic anemias of various types and secondary hemochromatosis

TREATMENT

The following discussion refers to the therapeutic management of patients with cirrhosis and mild-to-moderate hepatic insufficiency. The specific treatment of patients with hemochromatosis, hepatocellular degeneration, heavy metal intoxication or poisons, obstructive lesions of the extrahepatic biliary system, specific types of cirrhosis encountered in infants and children and hepatic coma is discussed in other sections. Management of cirrhosis, in general, consists of rest, dietotherapy, use of vitamins, hormones, antibiotics, lipotropic agents, antipruritic medications, abstinence from alcohol, specific measures employed to ameliorate intoxications from various heavy metals and other hepatotoxic drugs, and the control of electrolyte and water imbalances. The therapeutic goal in the management of cirrhosis should consist of (1) morphological evidence usually obtainable by needle biopsy such as disappearance of hepatocellular necrosis, fatty infiltration, stasis of bile and hepatocellular regeneration; (2) correction or stabilization of abnormal hepatic function tests or laboratory tests reflecting hepatic disease, and (3) amelioration of the patient's symptoms or physical findings indicative of hepatic insufficiency, portal hypertension or ascites.

The importance of bedrest has been emphasized in the management of patients with cirrhosis, ascites, asthenia, jaundice, fever, or gastrointestinal hemorrhage.[83, 109-111, 138, 209, 275, 278, 296, 318, 442-447, 623] When these clinical features disappear and cirrhosis is compensated or inactive, physical inactivity may only be curtailed. Restriction of physical activity and the optimum duration of bedrest is variable and may also depend on the patient's stamina and stabilization of hepatic function tests, particularly those indicative of hepatic insufficiency. Useful as a guide are the more sensitive tests of hepatic function such as the bromsulfalein, direct serum bilirubin, serum transaminase and serum cholinesterase. Bedrest, therefore, is prolonged in many patients with posthepatitic portal cirrhosis and postnecrotic cirrhosis and modified or abbreviated in patients with latent portal cirrhosis, biliary cirrhosis, hemochromatosis or hepatolenticular degeneration. Prolonged bedrest, on the other hand,

may be followed by mental depression, impaired appetite, weakness, loss of muscular tone, thrombophlebitis, stiffness of joints and infections, such as, cystitis, bronchopneumonia or stasis ulcerations. Consequently, bedrest should be individualized and ambulation recommended as soon as hepatic insufficiency or ascites improve. Bathroom privileges, on the other hand, should be advised if at all possible While the reason for the benefit derived from bedrest in cases of hepatic insufficiency is obscure, patients have been demonstrated to have a significant decrease in hepatic blood flow and an increase in hepatic metabolism during exercise or standing erect.[68-72, 134]

The effectiveness of adequate nutrition has been stressed as one of the most important therapeutic measures in managing the patient with cirrhosis The universally acceptable diet should consist of 2,500 to 4,000 calories, 80 to 120 gm of protein, 300 to 400 gm of carbohydrate, fat ad libitum, therapeutic amounts of vitamins and minerals, foods that are bland, nonirritating and nongaseous and, in patients with ascites or edema, restriction of sodium, usually in amounts of 0 5 to 1 0 gm. of sodium chloride daily. The daily caloric intake should be adjusted accordingly in patients with malnutrition or obesity. The benefits derived from dietotherapy in patients with cirrhosis have been disclosed by the amelioration of symptoms and physical findings, prolongation of estimated survival time, correction of abnormal hepatic function tests, and restitution of hepatic necrosis and hepatic regeneration as evidenced by needle biopsy of the liver (Table VI)[24, 29, 30, 109, 110, 138, 139, 167, 196, 256, 269, 275, 276, 298, 300, 302, 306, 319, 339, 402, 418, 420, 442-447, 473, 511, 591, 623] The results of many of these clinical investigations of the treatment of cirrhosis by a nutritious diet are subject to significant variation because of the lack of proper controls, study of small groups of patients, variable factors such as alcoholic withdrawal and bedrest, and inability to obtain adequate and necessary clinical follow-up The fecal loss of fat and, occasionally, nitrogen, increased urinary excretion of amino acids, faulty intermediate metabolism and loss of protein from repeated abdominal paracentesis have been emphasized to contribute to the malnutritive condition in patients with cirrhosis; however, the latter instance, does not explain satisfactorily malnutrition in pa-

TABLE VI

Clinical Course and Laboratory Data of a 40 year Old Male Alcoholic, Portal Cirrhosis Treated with a Low Sodium, High Caloric Diet

	Months		
Clinical Manifestations	*1*	*7*	*14*
Body weight lb	228	209	210
Jaundice	++	0	0
Ascites	++++	0	0
Edema	++++	0	0
Spider angioma	+	+	0
Palmar erythema	+	+	0
Hepatomegaly	7f	8f	2f
Splenomegaly	0	1f	0
Palmar erythema	+	+	0
Alopecia	+	+	+
Testicular atrophy	+	+	+
Laboratory Data			
Bilirubin, serum, D. I., mg. per 100 cc	2.1 / 3.1	.06 / 0.76	.03 / .26
BSP % retention in 45 min	35	8	9
Cephalin flocculation	4+	0	0
Thymol turbidity units	–	–	2.5
Zinc sulfate turbidity units	–	–	10.2
Prothrombin time %	46	–	100
Albumin, serum, gm. per 100 cc	3.0	4.3	5.5
Globulin, serum, gm. per 100 cc	3.2	2.4	2.5
Esophageal varices* (endoscopically)	+	+	0
Blood hemoglobin, gm. per 100 cc	10.8	16.2	16.7
WBC per cu. mm.	21,700	11,900	15,800
Sedimentation rate (Westergren)	102	15	12

*Note endoscopic disappearance of esophageal varices

tients with cirrhosis [139,104,166,167,214,215,217,244,308-311,582] Primary and secondary biliary cirrhosis are conditions characterized by steatorrhea and, occasionally, creatorrhea. Advanced cirrhosis of all types and hepatocellular degeneration disclose marked amino-aciduria. Cirrhosis is characterized commonly by marked loss of muscle and fat from the body, a large torso and emaciated extremities. Cirrhotic malnutrition is best explained by inadequate dietary intake.

Credit is due Patek and Post who were among the first investigators to recognize the clinical and prognostic virtue of a nutritious diet, rich in protein, supplemented by vitamin B complex in the management of patients with portal cirrhosis.[446] Most diets employed in the treatment of patients with cirrhosis exceed the recommended or necessary qualifications (Table VII, VIII). This is a basic diet supplying 2,000 to 2,500 calories daily containing between 70 and 100 gm. of protein and sufficient fat to make the diet palatable.[138] It has been recognized that protein is essential for hepato-

may be followed by mental depression, impaired appetite, weakness, loss of muscular tone, thrombophlebitis, stiffness of joints and infections, such as, cystitis, bronchopneumonia or stasis ulcerations Consequently, bedrest should be individualized and ambulation recommended as soon as hepatic insufficiency or ascites improve. Bathroom privileges, on the other hand, should be advised if at all possible While the reason for the benefit derived from bedrest in cases of hepatic insufficiency is obscure, patients have been demonstrated to have a significant decrease in hepatic blood flow and an increase in hepatic metabolism during exercise or standing erect.[65-72, 134]

The effectiveness of adequate nutrition has been stressed as one of the most important therapeutic measures in managing the patient with cirrhosis The universally acceptable diet should consist of 2,500 to 4,000 calories, 80 to 120 gm. of protein, 300 to 400 gm. of carbohydrate, fat ad libitum, therapeutic amounts of vitamins and minerals, foods that are bland, nonirritating and nongaseous and, in patients with ascites or edema, restriction of sodium, usually in amounts of 0 5 to 1 0 gm. of sodium chloride daily. The daily caloric intake should be adjusted accordingly in patients with malnutrition or obesity The benefits derived from dietotherapy in patients with cirrhosis have been disclosed by the amelioration of symptoms and physical findings, prolongation of estimated survival time, correction of abnormal hepatic function tests, and restitution of hepatic necrosis and hepatic regeneration as evidenced by needle biopsy of the liver (Table VI)[24,29, 30, 109,110, 134, 139, 167,196, 236, 240, 275, 276, 296, 300, 302, 306, 319,330,403, 418, 420, 442-447,473,512,591, 623] The results of many of these clinical investigations of the treatment of cirrhosis by a nutritious diet are subject to significant variation because of the lack of proper controls, study of small groups of patients, variable factors such as alcoholic withdrawal and bedrest, and inability to obtain adequate and necessary clinical follow-up. The fecal loss of fat and, occasionally, nitrogen, increased urinary excretion of amino acids, faulty intermediate metabolism and loss of protein from repeated abdominal paracentesis have been emphasized to contribute to the malnutritive condition in patients with cirrhosis; however, the latter instance, does not explain satisfactorily malnutrition in pa-

TABLE VIII
Clinical Course and Laboratory Data of a 39 year old Male with Posthepatitic Portal Cirrhosis
(Hepatitis 3 months after yellow fever vaccination, 1942)

Clinical Manifestations	*May 1953*	*Sept 1953*	*Dec 1953*	*July 1954*	*Aug 1955*	*Jan 1956*
Body weight, lb	146	177	175	174	178	180
Emaciation	+	0	0	0	0	0
Abdominal pain	+	0	0	0	0	0
Jaundice	0	0	0	0	0	0
Pruritus	0	0	0	0	0	0
Spider angiomata	+	+	+	+	+	+
Palmar erythema	+	+	+	+	+	+
Alopecia	0	0	0	0	0	0
Hepatomegaly	0	0	0	0	0	0
Splenomegaly	2+	2+	2+	2+	0	0
Ascites	0	0	0	0	0	0
Edema	+	0	0	0	0	0
Varices (endoscopically)	0	+	+	+	+	+
Laboratory Data						
Bilirubin, serum mg per 100 cc	.16/.91	.21/1.72	.21/1.13	.15/.85	.06/1.2	.02/1.0
BSP retention % in 45 min	21	9	11	10	6	5
Cephalin flocculation	3+	3+	3+	1+	1+	1+
Thymol turbidity	–	–	–	–	7	7
Prothrombin time %	52	46	100	46	67	100
Albumin serum, gm per 100 cc	3.8	4.8	4.9	3.9	3.5	3.6
Globulin serum gm per 100 cc	3.3	3.2	3.0	2.6	4.0	3.9
Hemoglobin gm per 100 cc	13.7	–	16.9	11.9	15.4	11.8
RBC x 10⁶ per cu mm	4.33	–	–	–	4.98	4.62
WBC per cu mm	6200	–	5700	6200	5000	6200
Platelets per cu mm	320000	–		350000		300000
Sedimentation rate (Westergren)	45	–	7	6	10	8

Treatment 150 gm protein 400 gm carbohydrate diet, vitamins rest

intake of the cirrhotics This, however, may produce sufficient nausea, vomiting, diarrhea, constipation and flatulence to further decrease the total caloric intake and, secondly, this hyperalimentation is potentially dangerous in hepatic insufficiency because of intoxication from proteins Feeding by gastric intubation may be necessary in the anorexic patient

Vitamins to supplement the diet in the management of patients with cirrhosis have been in vogue Actually, avitaminosis is not found too commonly in patients with cirrhosis and a nutritious diet provides sufficient amount of vitamins [25,34,45,233,238,179,421,623] The outstanding exceptions are fat-soluble vitamin K which should be administered intramuscularly as an aqueous preparation in an

TABLE VII

CLINICAL COURSE AND LABORATORY DATA OF A 45-YEAR-OLD MALE WITH SERUM HEPATITIS PROGRESSING TO A POSTHEPATITIC CIRRHOSIS

Clinical Manifestation	*11 9-54*	*1 11-55*	*3-6-55*	*6-19 55*	*1 15 56*
Body weight lb	123	156	167	181	182
Jaundice	+	+	0	0	0
Ascites	0	0	0	0	0
Edema	0	0	+	+	0
Hepatomegaly	6f	2f	2f	0	0
Splenomegaly	1f	1f	0	0	0
Weakness	+	+	0	0	0
Pruritus	+	+	0	0	0
Laboratory Data					
Bilirubin, D/T, mg per 100 cc	7 4/12 1	1 4/2 9	0 11/0 58	0 09/0 58	0 01/0 26
Alk phosphatase, Bodansky units	2 3	3 4	1 6	1 8	2 16
BSP % retention 45	—	38	3	1	1
Cholesterol mg per 100 cc	185	231	320	310	318
Cholesterol esters mg per 100 cc	80	102	140	154	182
Cephalin flocculation	3+	2+	3+	1+	0
Thymol turbidity, units	25 2	19 1	20 9	15 7	13 1
Zinc sulfate turbidity, units	26 4	26 2	21 0	20 4	18 2
Albumin, gm per 100 cc	3 8	3 9	4 1	3 9	4 1
Globulin, gm per 100 cc	4.5	4 5	3 3	2 8	3 1
Prothrombin time %	50	93	100	100	64
Sedimentation rate (Westergren)	80	52	38	41	33

Treatment 200 gm protein, 500 gm carbohydrate
Fat Ad Lib Diet, Vitamins, rest

cellular recovery[459] Certainly this diet supplemented with therapeutic vitamins can be tolerated by most cirrhotics with the exception of those in severe hepatic failure The dietary ingredients should be increased as the patient's appetite improves Restriction of dietary fat is unnecessary except in cases with hepato-biliary steatorrhea, in which case supplementary administration of oral bile salts is recommended (Table IX).[123,547,618] It has been demonstrated that diets high in content of fat are harmless to the liver[405]

The patient with cirrhosis can be administered nutrients parenterally, particularly, if anorexia is pronounced. Hyperalimentation may be in the form of hypertonic glucose, albumin, or protein hydrolysates administered intravenously. These methods have never been too popular, except in the unusual case, because of thrombophlebitis, nausea, vomiting and fever which may be complicating features. The caloric requirements rendered in this manner are never adequate and tend to interfere with oral nourishment. Oral dietary supplements may be advocated to increase the caloric

(Table VI). The physician should make every effort to discuss firmly the "poisonous" role of alcohol with a patient who has cirrhosis, and to emphasize that one drink may eventually perpetuate an alcoholic debauch. While the physician treating an alcoholic with portal cirrhosis should employ elementary psychotherapeutic measures, it may be necessary to recommend consultation and treatment by a qualified psychiatrist, alcoholic treatment center, Alcoholics Anonymous, or the Mental Hygiene Clinic. The management of cirrhosis is difficult enough without the physician's sincere and sympathetic insistence on the patient's abstinence from alcohol. One should never forget that, fundamentally, the alcoholic with portal cirrhosis has an emotional, environmental or hereditary problem.[425,510] Alcoholics are recognized to possess a low tolerance of anxiety, and psychotherapy alone may prove an unsuccessful task. The medical management of patients with cirrhosis due to specific hepatotoxic agents such as phosphorus, arsenicals or chloroform is preventative. Cirrhosis associated with heavy metal poisonings such as arsenicals usually involves a lesion too advanced to be benefited by BAL therapy.

Hormones are considered beneficial in the management of patients with cirrhosis in certain situations. Methyl testosterone and testosterone proprionate have been employed therapeutically with limited success for their protein anabolic effect in the nutritional management of cirrhotics.[212,265,305,501,520,534] The therapeutic use of corticotropin or adrenal steroids in patients with cirrhosis has been disappointing. The administration of these drugs may ameliorate the patient's condition, improve his appetite, diminish jaundice and be associated with transient improvement in some hepatic function tests, particularly those pertaining to acute hepatocellular damage as the bromsulfalein, direct serum bilirubin, serum alkaline phosphatase, serum transaminase and serum cholinesterase, such as observed particularly in patients with postnecrotic cirrhosis, posthepatitic portal cirrhosis, and primary biliary cirrhosis (Table IX). However, once this therapy is discontinued, clinical and biochemical relapses occur and the course of the disease is unaltered.[3,53,54,55,63,65,86,262,527-529,582,583,673,693] In general, the use of corticosteroids in the treatment of various types of hepatic disease has

TABLE IX
EFFECT OF THE ADMINISTRATION OF ORAL BILE SALTS UPON THE AMOUNT OF STEATORRHEA AND AZOTORRHEA IN A PATIENT WITH POSTOPERATIVE STRICTURE OF THE COMMON BILE DUCT

Stool	*Normal*	*Days*	*3**	*17*	*26*
Quantitative fat, 24 hr.	(1·5 gm)		11 7	6.2	10.2
Quantitative nitrogen, 24 hr	(1·2 gm)		2 4	1 8	2 0

*Eight grams of bile salts administered orally per day from the fourth to twentieth days

amount of 5 mg. daily Vitamin A, D and K are necessary therapeutic adjuncts in cases with hepatobiliary steatorrhea, and large doses of the vitamin B-complex administered to patients with advanced hepatic insufficiency or coma

The lipotropic agents, choline, methionine and inositol, in particular, contribute little nutritionally and may be harmful to the patient with cirrhosis subsisting on a balanced diet [139,167,212,213, 296 305,309-311,319,623] An optimum diet containing 100 gm of protein employed in the management of cirrhosis furnishes approximately 2 8 gm. of methionine and 0.9 gm. of choline. Much of the enthusiasm for the use of these agents originates from their beneficial role in experimental hepatic disease, particularly fatty livers. In any event, they should be employed only in patients with fatty infiltration of the liver or fatty cirrhosis, particularly if the patients avoid a nutritious diet [29,30,103-105,130,158,212,213,480,588,627] Methionine or choline in a dose of 1.0 gm. four times daily is recommended in these cases On the other hand, methionine toxicity and the possible role played by methionine in the pathogenesis of hepatic coma in patients with diseases of the liver has been recognized [309,310,438,566 612 614,658] Finally, despite earlier enthusiastic reports, large doses of liver extract administered intravenously or in oral preparation are not considered a necessary therapeutic adjunct.[348 349,493]

Imbibition with alcohol should be ceased not only in alcoholics with portal cirrhosis but in all patients with cirrhosis [17,48,124,139,273, 293,319,459,595,605] While alcohol probably plays a minor role, if any, in the pathogenesis of portal cirrhosis, it is known to be hepatotoxic experimentally and to interfere with proper dietary habits so necessary in the restoration of nutrition in the cirrhotic individual

(Table VI) The physician should make every effort to discuss firmly the "poisonous" role of alcohol with a patient who has cirrhosis, and to emphasize that one drink may eventually perpetuate an alcoholic debauch. While the physician treating an alcoholic with portal cirrhosis should employ elementary psychotherapeutic measures, it may be necessary to recommend consultation and treatment by a qualified psychiatrist, alcoholic treatment center, Alcoholics Anonymous, or the Mental Hygiene Clinic. The management of cirrhosis is difficult enough without the physician's sincere and sympathetic insistence on the patient's abstinence from alcohol. One should never forget that, fundamentally, the alcoholic with portal cirrhosis has an emotional, environmental or hereditary problem.[420 510] Alcoholics are recognized to possess a low tolerance of anxiety, and psychotherapy alone may prove an unsuccessful task. The medical management of patients with cirrhosis due to specific hepatotoxic agents such as phosphorus, arsenicals or chloroform is preventative. Cirrhosis associated with heavy metal poisonings such as arsenicals usually involves a lesion too advanced to be benefited by BAL therapy.

Hormones are considered beneficial in the management of patients with cirrhosis in certain situations. Methyl testosterone and testosterone proprionate have been employed therapeutically with limited success for their protein anabolic effect in the nutritional management of cirrhotics.[213 265 304 501 520 534] The therapeutic use of corticotropin or adrenal steroids in patients with cirrhosis has been disappointing. The administration of these drugs may ameliorate the patient's condition, improve his appetite, diminish jaundice and be associated with transient improvement in some hepatic function tests, particularly those pertaining to acute hepatocellular damage as the bromsulfalein, direct serum bilirubin, serum alkaline phosphatase, serum transaminase and serum cholinesterase, such as observed particularly in patients with postnecrotic cirrhosis, posthepatitic portal cirrhosis, and primary biliary cirrhosis (Table IX). However, once this therapy is discontinued, clinical and biochemical relapses occur and the course of the disease is unaltered.[3 53 54 55 63-65 86 205 527-529 582 593 673 693] In general, the use of corticosteroids in the treatment of various types of hepatic disease has

been disappointing, except for the occasional patient with acute hepatitis or postnecrotic cirrhosis by modifying the symptoms and *hepatic function tests when hepatic insufficiency* ensues (Tables II, V, X, XI) Its use in the treatment of cirrhosis with ascites or edema has been unsuccessful except for the unusual case in which diuresis occurs *following cessation of steroid therapy* [91] Untoward effects of corticosteroid therapy such as anasarca, mental depression, euphoria, psychosis, peptic ulcer, acute pancreatitis, thrombophlebitis, features of Cushing's disease, diabetes mellitus, coma and death are mentioned to emphasize the hazards of administering *these medications to patients with cirrhosis. In the event this type* of treatment has been employed, the initial and maintenance doses per day of a corticosteroid vary and may be prescribed as follows: *cortisone orally, 200 mg and 75-50 mg., prednisone or prednisolone*

TABLE X

CLINICAL AND LABORATORY DATA IN A CASE OF POSTHEPATITIC CIRRHOSIS TREATED WITH STANDARD REGIMEN AND ACTH

Laboratory Data		*1953*	*Date* *Early 1954*	*Late 1954*	*1955*
	D 0.2	1 39	1.28	0 16	0 17
Serum bilirubin, mg /100 cc	T 1.5	3 47	3 06	0 78	1 00
BSP % 45 min	*0*	*32*	*37*	*32*	17
Serum albumin, gm /100 cc	3 6 5 4	3 0	4 4	3 6	3 8
Serum globulin, gm./100 cc	1 5-3 4	3 9	3.2	2 7	2 6
Ceph flocc 48 hr	0 1+	1+	4+	2+	2+
Prothrombin time, % of normal	100	50	73	—	—
Sedimentation rate (Westergren)	0-10	30	30	40	40
Blood hemoglobin, gm /100 cc		11.2	13 1	14 1	13 7
RBC × 10^6 per cu mm		3 90	4.25	—	4 38
WBC per cu mm		*3000*	*5850*	*5100*	8350
Platelets per cu mm.		184,800			
*Clinical Manifestations**					
Jaundice (0—++++)		+	+	*0*	*0*
Edema		*0*	*0*	*0*	+
Ascites		*0*	*0*	*0*	0
Spider angioma		+	+	+	+
Pruritus		*0*	*0*	*0*	0
Body weight		*140*	*130*	151	156
Asthenia		+	+	0	0
Enlarged liver		3f	0	0	0
Enlarged spleen		*2f*	*2f*	*2f*	2f
Treatment	High protein, high caloric diet, vitamins, bedrest		ACTH 40 *cc /day*	Diet & Vitamins	ACTH stopped

*Infectious hepatitis in 1952

TABLE XI

Clinical Course and Laboratory Data of a 55 Year Old Female with Postnecrotic Cirrhosis and Hypersplenism

	Date								
Clinical Manifestations	4-23-52	4-13-53	10-12-53	10-27-53	4-21-54	10-18-54	2-19-55	6-12-55	11-16-55
Body weight, lb	129	120	120	150	135	140	150	132	132
Emaciation	0	0	0	0	0	0	0	0	0
Jaundice	0	0	+	+	+	+	+	+	+
Pruritus	0	0	+	+	+	+	0	+	+
Skin melanosis	0	0	0	+	+	+	+	+	+
Bone pains	0	0	0	0	0	0	0	0	0
Ascites	0	0	1+	0	0	1+	0	0	0
Edema	0	0	1+	0	0	1+	0	0	0
Alopecia	0	0	1+	0	0	1+	0	0	0
Spider angioma	0	0	0	+	0	0	+	+	+
Palmar erythema	0	0	0	+	0	0	+	+	+
Hepatomegaly	0	2+	1+	3+	3+	1+	3+	3+	3+
Splenomegaly	0	1+	2+	2+	2+	2+	2+	3+	3+
Varices (esophagoscopically)	0	—	+	+	+	+	+	+	+
Laboratory Tests									
Bilirubin serum mg per 100 cc	—	0.4/1.0	2.0/3.8	1.0/1.6	1.8/4.2	1.7/3.8	2.2/3.2	6.4/10.6	—
Alk phosphatase plasma Bodansky units	—	32.3	36	—	31	20	—	—	—
BSP retention %, 45 min	—	33	40	31	35	16	—	—	—
Cholesterol plasma mg per 100 cc	—	168	155	—	—	—	—	—	—
Cephalin flocculation	—	1+	3+	0	—	—	—	—	—
Prothrombin time %	—	100	50	—	—	—	—	—	—
Hemoglobin blood gm per 100 cc	13.5	12.6	11.9	12.3	—	13.7	12.6	10.8	—
RBC per cu mm × 10⁴	458	455	371	411	—	—	—	—	—
WBC per cu mm	7950	5500	8500	9500	—	6800	5100	7100	—
Platelets per cu mm	—	—	60,000	—	—	—	139,700	—	—
Albumin, serum gm per 100 cc	—	4.7	4.0	2.6	3.9	3.7	—	3.2	—
Globulin serum gm per 100 cc	—	2.3	2.7	3.0	2.9	2.6	—	2.6	—
Sedimentation rate (Westergren)	35	45	92	120	84	—	75	84	—
Clinical Course	Diarrhea	Diarrhea Abd pain	Hematemesis		Intractable pruritus			Intractable pruritus	
Treatment	High protein High carbohydrate Fat ad lib diet Vitamins, Rest		Portacaval shunt					Methyl Testerone administered Pruritus relieved Jaundice intensified	

orally, 80 mg. and 20 mg; triamcinolone, 20 mg. and 4 mg; methylprednisolone, 16 mg. and 4 mg, hydrocortisone intramuscularly, 150 mg. and 40 mg.; and corticotropin intramuscularly, 100 units and 40 units. Actually, in some clinics, huge doses of steroids, e.g., 100 mg. of ACTH gel daily, or 1.0 gm. of cortisone, are administered for forty-eight weeks or until remission of hepatic insufficiency occurs, as may be observed in patients with postnecrotic cirrhosis. The administration of sodium-restricted diets and potassium chloride by mouth, 4 0 gm. daily in divided doses, is advisable when these steroids are prescribed, with the possible exception of prednisone or prednisolone or their derivatives

The management of intractable pruritus present in patients with primary or secondary biliary cirrhosis, in particular, is symptomatic in view of its obscure pathogenesis. The most effective treatment is methyl testosterone administered sublingually, but this substance is icterogenic and masculinizing (Table XI) [322,353,562,664] Occasionally, an antihistaminic agent, phenobarbital, ergotamine tartrate, reserpine and corticosteroids administered orally or parenterally, alone or in combination, corn starch or oatmeal baths, methyl or phenol lotions, intramuscular adenosine 5-monophosphate, or antihistaminic or topical anesthetic inunctions are beneficial [109,431,450,582] None of these therapeutic measures are effective consistently in the management of pruritus in patients with hepatocellular or obstructive jaundice Relief of obstructive lesions of the extrahepatic bile by T-tube drainage or surgical side-tracking of the common bile duct may lead to relief of pruritus in patients with secondary biliary cirrhosis The advent of marked hepatic insufficiency in one patient with primary biliary cirrhosis coincided with relief of pruritus. Vitamin B_{12} or the local infiltration of heparin into xanthomata may be beneficial in dissolving cutaneous lesions in patients with biliary cirrhosis [131,513]

Antibiotics of choice are recommended in the management of specific bacterial infections complicating patients with cirrhosis. Sedation and hypnosis are best managed by the administration of phenobarbital or barbital because these substances are mostly excreted by the kidney. It is best not to use other sedatives, hypnotics or narcotics for fear of precipitating coma in the event of hepatic

insufficiency.[93, 94, 159, 531] The specific dangers ascribed to barbiturates in patients with cirrhosis, according to some observers, appear to be overemphasized.[651] The macrocytic anemia observed in patients with cirrhosis may be corrected better by nutritious diet than by the administration of liver extract, vitamin B_{12} or folic acid. Transfusions of blood, parenteral iron preparations or iron administered orally may be employed to treat iron-deficiency anemia as the result of loss of blood in patients with cirrhosis. An ambulatory ulcer diet or a bland diet complimented by a gastric antacid prescribed between meals and at bedtime is recommended in the elective medical management of esophageal varices in order to prevent peptic erosion.

HEPATIC COMA

The neurophychiatric comatose state, usually occurring terminally in patients with hepatic insufficiency due to acute or chronic diffuse parenchymal damage of the liver has been referred to as hepatic coma. Actually, the term, hepatic coma, has limited connotation, inasmuch as many patients with hepatic insufficiency demonstrate an altered intellect and personality instead of or prior to coma. Hepatic coma should always be regarded diagnostically for the present as a clinical condition. The syndrome of hepatic coma was recognized by Galen, Celsus and Hippocrates, the latter who said, "those who are mad on account of phlegm are quiet, but those on account of bile are vociferous, vicious and do not keep quiet."[108, 271] In 1769 Morgagni described hepatic coma in a priest in whom restlessness and stupidity progressed to delirium and convulsions, then coma and death.[459] Hepatic coma occurring in patients with cirrhosis was recognized by Bright in 1836 and Budd in 1845 and Copeland in 1858.[75, 50, 137] In 1860, Frerichs described in his monograph, *A Clinical Treatise on Disease of the Liver*, the neuropsychiatric features of hepatic coma or "acholia," as he named it, occurring in a series of patients who died from cirrhosis or acute yellow atrophy.[210] During this time, acholia or cholemia was employed to describe hepatic coma inasmuch as coma was considered due to the retention of bile in the blood in patients with hepatic insufficiency. Adams and Foley in 1953 studied 60 patients with

hepatic coma and documented classically the neuropsychiatric features of this condition.[1] They emphasized the state of confusion and inappropriate behavior which preceded coma, muscular rigidity, hyperreflexia, flapping tremor of the arms and a characteristic electroencephalographic pattern in patients with hepatic insufficiency, most of whom *had cirrhosis of some type.*

PREDISPOSING FACTORS AND PATHOGENESIS

Hepatic coma may occur spontaneously or be the result of or associated with various predisposing or complicating factors in patients with different types of hepatic disease These diseases are principally cirrhosis, hepatitis, or metastatic invasion of the liver, and, less commonly, cholestatic hepatic disease, abscess, fatty infiltration of the liver and various infiltrative or granulomatous hepatic diseases the conditions or agents which can precipitate hepatic coma in patients with cirrhosis include the following: alcoholism, gastrointestinal hemorrhage; infections, neoplasms *including cerebral metastasis, drugs, such as, hyponotics*, sedatives, narcotics, ammonium salts or ammonium-containing cation-exchange resins, diuretic agents, methionine, sulfonamides, abdominal paracentesis, fluid and electrolyte imbalance; surgical operations; anesthesia, fever, diets containing protein or intravenous protein hydrolysate, portacaval shunt; transfusions of blood and congestive heart failure (Table XII).[12,40,73,95,101,133,197,274,201,210,237,295,302,349,371,392,398,423,429,440,455,466,528,548,551,562,564,593,594,610,632,650,659] *It is apparent* that stress of any type or an iatrogenic component may induce or contribute to the production of hepatic coma suggesting the abnormally sensitive metabolic relationship between the liver and brain in patients with parenchymal hepatic disease.

It has been observed that when hepatic coma ensues, its occurrence is spontaneous in half of the patients with cirrhosis (Table XIII) Hepatic coma occurs, particularly as the result of massive gastrointestinal hemorrhage, infections, abdominal paracentesis, anesthesia or surgical operations in the remaining half of patients *with cirrhosis These conditions may induce further* hepato-

TABLE XII
RESULTS OF VARIOUS HEPATIC FUNCTION TESTS IN A PATIENT WITH PORTAL CIRRHOSIS IN IMPENDING HEPATIC COMA

	Normal	Days 1	Days 5	Days 11	
Serum bilirubin, direct/total mg per 100 cc	0.2/1.0	21.7/42.2	11.3/21.4	11.4/20.6	
Serum albumin/globulin, gm per 100 cc.	3.5/2.5	3.0/3.2	2.6/2.9	3.5/2.4	
Blood urea nitrogen, mg per 100 cc	8-15	67	—	15	
Cephalin Cholesterol flocculation 24 hr	0, 1+	2+	—	2+	
Thymol turbidity, units	0-7	7.4	—	6.8	→ survival
Zinc sulfate turbidity, units	5.5-10.5	8.9	—	8.6	
Alkaline phosphatase bodansky units	1.5-4.0	5.6	—	3.5	
Prothrombin time, %	100	34	—	47	
Serum transaminase (SGO-T) micromols per 100 cc	33-119	358	424	336	
Serum cholinesterase Δdelta pH units per 100 cc	0.5-1.2		0.23	0.24	
Blood ammonia γg per 100 cc	0.05-0.33	7.3	4.0	4.0	

Treatment Conventional protein restriction prednisone administered on the 3rd day

ing alcohol and chloroform diminished arterial or portal blood flow to the liver as the result of shock, surgical operations including shunt procedures or abdominal paracentesis have all been implicated in the production of hepatic dysfunction [10, 69, 73, 140, 149, 177, 295, 361, 398, 423, 437, 515, 669]

Bacterial and viral infections are common precipitating factors in the production of hepatic coma in patients with hepatic disease This may be due to fever which is known to produce hepatocellular necrosis, reduction of blood and oxygen supply to the liver, or possibly bacterial or toxic products reaching the liver via the portal vein [37, 250, 267, 323, 371, 511, 654] The liver is known to be a major site for the removal of bacteria, though little is known as to what toxic effects, if any, that bacteria have upon the liver [37]

Electrolyte and water imbalances and injudicious or unnecessary diuresis or abdominal paracentesis have been recognized to contribute to or produce hepatic coma In particular, hyponatremia and hypochloremia resulting from overhydration, sodium-restricted diets, drug-induced diuresis, or abdominal paracentesis may manifest itself in the low-sodium syndrome, in which apathy,

TABLE XIII

CLINICAL AND LABORATORY DATA OF 57-YEAR-OLD MALE WITH ALCOHOLIC PORTAL CIRRHOSIS, ASCITES AND BLEEDING ESOPHAGEAL VARICES

		4/29	5/1	5/3	5/7	5/8	5/10	5/12
Serum bilirubin mg /100 cc D/T	0 2/1 5	0 3/1 4		1 1/3 4		7 2/11 9		11 4/16 1
Alk phosphatase (Bodansky units)	2 4	4 7				5 3		8 4
BSP % 45 min	0	21			31			
Blood cholesterol mg /100 cc	130 300	157		164	142			154
Serum albumin gm /100 cc.	3 6 5 4	2 3		2 1	1 9			1 7
Serum globulin gm /100 cc	1 5-3 4	3 0		3 1	3 3			3 2
Ceph flocc 48 hrs	0-1+	3+		3+	3+		4+	4+
Prothrombin time % of normal	100	50		67	73	50		38
Blood hemoglobin gm /100 cc		9 3	10 1	11 5	7 8	11 2		7 0
Hematocrit % RBC		31	33	37	29	35	35	25

RBC/cu mm x 10⁶	3.24	4.10		3.21			2.75
WBC/cu mm	3200	3100		12,400			32,000
Platelets per cu mm	214000						232000
Hematemesis	1000 cc	1500 cc	0	0	0	0	0
Melena	+	+	0	0	+	+	+
Blood pressure, mm Hg	86/60	70/?	110/72	115/81	104/74	94/60	40/?
Ascites, grade	4+	4+	4+	1+	1+	1+	2+
Edema, grade	2+	2+	2+	2+	2+	2+	2+
Jaundice, grade	0	0	0	1+	2+	2+	3+
Coma	0	0	0	0	0	+	+
Procedures	1 Transfused 1500 cc blood 2 3000 cc 15% glucose 3 Oxygen tent → 4 Esophageal tamponade balloon → 5 Vitamins →	1 Transfused 2000 cc blood 2 2000 cc 15% glucose	1 Surgical ligation of splenic and left gastric artery and coronary vein 2 Tranfused 2000 cc blood → → →	1 Abdominal paracentesis of 2100 cc	1 Insertion Crosby Cooney button 2 Transfused 1500 cc blood 3 1500	1 Fever 2 Aureomycin I.M. 3 Transfused 1000 cc. blood	1 Death
					← Attempted correction of → mild hypochloremic, normonatremic, hypokalemic acidosis and fluid loss		

drowsiness, confusion, psychosis, coma, weakness, cramps and twitchings are central nervous and muscular features (Table XII). Biochemical abnormalities such as hypokaliemia, low-serum magnesium, hypophosphatemia and respiratory alkalosis may play a minor contributory role in the pathogenesis of hepatic coma; however, correlation between these biochemical abnormalities and hepatic coma is lacking[12,16,101,173,460,512,545,609]

Acetozolamide, an oral diuretic, which is an effective diuretic agent in patients with hepatic disease, also has been demonstrated to contribute to hepatic coma[322,512,635] Diuresis with mercurials is known to produce depressed concentrations of sodium, potassium, and chloride particularly, and also metabolic alkalosis. For this reason, the concurrent administration of calcium and potassium chloride during mercurial diuresis is advisable.[306,464,512,522]

Hepatic coma has been attributed to elevation of pyruvic, lactic and amino acids in patients with hepatic insufficiency[11,21,58,81,101,150,152,574,633,690] Impaired carbohydrate intermediary metabolism in these patients, particularly the formation of cocarboxylate from thiamine, may explain high lactic pyruvic acid levels[672] Cerebral anoxia, decreased cerebral oxygen consumption, and respiratory alkalosis have been suggested as contributing to the metabolic defect in patients with hepatic coma[615,660] However, none of these metabolic abnormalities satisfactorily explain the pathogenesis of hepatic coma. The main possible exception is the role of abnormal ammonium metabolism The patient with hepatic insufficiency is not unlike one with myocardial disease in that the reduction of blood supply and oxygen perpetuates cellular necrosis Hepatic coma has been recognized to be precipitated or aggravated by hypnotics, sedatives, anesthetic agents, analgesic drugs and narcotics.[43,93,94,137,153,244,297,302,326,347,423,481,504,512,731] It is advisable to use discrimination employing these drugs in small amounts for any patient with hepatic disease Opiates, paraldehyde, methodon, chloryl hydrate and most barbiturates are highly dangerous and should never be employed therapeutically in patients with marked hepatic insufficiency mainly because of their depressive respiratory effects and perpetuation of their effects and persistence of the drug in the blood due to impairment of detoxification and excretion by the injured liver The selection of a proper sedative, analgesic or

hypnotic agent in the management of a patient with hepatic insufficiency presents a problem. Generally, phenobarbital or barbital are advocated because they are excreted to a great extent by the kidney. Demerol, if used discriminately, is considered a safe analgesic agent in this condition, but should be administered cautiously in small doses (25 mg) Intramuscular chloropromazine or perphenazine in a dose of 5 to 10 mg, appears to be safe in the management of hepatic coma[641,319] The injurious effect of anesthetic agents upon the diseased liver also should not be overlooked Chloroform has been shown to be hepatotoxic, and sodium pentothal highly inadvisable in the presence of hepatic injury.[161,229,230,403,404,435] Spinal anesthesia is probably the safest method of anesthesia and ether nitrous oxide or cyclopropane are reasonably safe anesthetic agents to be employed during an operative procedure in patients with hepatic disease provided adequate oxygen is administered and arterial blood pressure maintained [156,209,229,230,499]

In the past fifteen years there has been an increased interest in the pathogenetic roles of protein, enterogenous nitrogenous substances and ammonia in hepatic coma Bollman and Mann disclosed elevation of ammonia and decrease of urea in the blood of hepatectomized animals[59,60] Bilateral nephrectomy, on the other hand, performed simultaneously with a hepatectomy did not alter significantly the concentration of urea in the blood These experiments demonstrated that the liver was capable of deamination of amino acids and that urea was formed in the liver from ammonia. Following hepatectomy, an Eck fistula, or experimental hepatic injury, protein alimentation was demonstrated to be lethal, a phenomenon called "meat intoxication."[58,59,165,252,410,449]

Elevated ammonia concentration in the blood was found presumably due to absorption of nitrogenous substances from the intestines In the presence of hepatic injury, an Eck fistula or a hepatectomy, ammonia produced in the intestinal tract by urea-splitting bacteria (urease) is absorbed into the portal vein, but is not metabolized enzymatically to urea Consequently, ammonia intoxication leading to death has been produced experimentally in this manner and also by the administration of exogenous ammonium salts

Similarly, it has been demonstrated in humans with hepatic

diseases with natural or surgical portacaval shunts that the administration of protein, urea or ammonium salts in one form or another induces a syndrome resembling hepatic coma in which there exists high levels of blood ammonia [49,111,216,221,302,390-392,424,460,562,564,597,603,610,659] Elevated blood ammonia and alpha-keto glutarate levels have also been demonstrated in patients with cirrhosis in hepatic coma and, occasionally, in cirrhotics without hepatic coma.[82,85,211,510,545,548,609,632] Interference with the intermediary metabolism involving the Kreb's cycle and the vitamin B-complexes and failure of the diseased liver to form necessary metabolic products have also been considered as pathogenetic factors [49,71,85,574] However, the correlation between the concentration of ammonia in the blood and the mental state of patients with cirrhosis is inconsistent and, as a consequence, some other biochemical explanation of hepatic coma besides ammonia intoxication is readily apparent (Table XII).[85,137,168,170,322,345,548] The correlation is better in patients with hepatitis, particularly children, and may be indicative of the tremendous reserve capacity of urea synthesis Impaired hepatic function and the association of collateral portal venous circulation, which diverts portal blood containing a high concentration of ammonia and nitrogenous substances into the systemic circulation, have been considered important in the pathogenesis of hepatic coma [563,564,591] This implies the existence of an endogenous or spontaneous type of hepatic coma, about which little is known It appears to be related to hepatocellular necrosis rather than directly to elevated blood ammonia values Treatment is less specific and the prognosis not as favorable Despite this inadequate explanation of the pathogenesis of hepatic coma, it is unquestionably obvious that the administration of urea, ammonium salts and dietary protein to patients with cirrhosis and hepatic insufficiency may provoke hepatic coma or a similar syndrome. As a result of these findings hepatic coma has been divided into two types, the exogenous and endogenous type. The former is observed in patients with hepatic disease, following a portacaval shunt, gastrointestinal hemorrhage, or the administration of protein or protein hydrolysates and may even occur in the absence of hepatic disease. It is related directly to hyperammoniumemia and has a fair prognosis In hepatic disease,

protein or blood is digested by urease and aminoacidoxidase intestinal enzymes and increased amounts of ammonia are absorbed into the portal blood stream.[637] This condition may also occur as the result of naturally occurring or artificial portacaval shunts, endogenously administered ammonium salts or as the result of acetozolomide (Diamox®) administration. The latter drug inhibits the renal excretion of ammonia in the dog. The mechanism of exogenous hepatic coma is hyperammoniumemia with interference of the urea and adenosine triphosphate, arginine and glutamine metabolism.

In view of this, the role of glutamine metabolism has been studied in patients with hepatic coma. Glutamine, formed in the liver enzymatically by the combination of glutamic acid and ammonia, has been demonstrated by some observers to be increased in the brain, blood and cerebrospinal fluid in experimental hepatectomized animals and in humans with hepatic coma.[47, 59-60, 632-634] *Others have noted little correlation between hepatic coma and the* level of blood glutamine.[549] Diverse correlation has been demonstrated between elevated arterial ammonia and pyruvate levels and cerebral oxygen utilization.[85, 189, 190] Bessman has stated that blood ammonia levels are unreliable prognostically in hepatic coma. Both the brain and skeletal muscles metabolize ammonia.[47] Enterogenous toxins other than ammonia may induce hepatic coma, and it is important to consider what chemical is absent rather than excessive in the brain of a patient in hepatic coma. Nevertheless, the administration of glutamic acid therapeutically in an effort to neutralize the elevated blood ammonia concentration in patients with hepatic coma has been advocated as a therapeutic trial.

Bessman has studied the role of serotonin or 5-hydroxyindole acetic acid in hepatic coma.[46] It has been noted that 5-dihydrotryptophane, a precursor of serotonin, is not synthesized by the diseased liver, and treatment of hepatic coma with this substance altered the abnormal electroencephalographic pattern.

PATHOLOGICAL MANIFESTATIONS

Information derived from necropsies in patients who died in hepatic coma discloses no specific pathological lesion in any of the

organs of the body This would appear to indicate that hepatic coma results from a metabolic abnormality rather than from a specific lesion in the liver, brain or kidney The morphological manifestations of any type of cirrhosis in a patient who has died from hepatic coma do not differ from those demonstrated when cirrhosis is latent or associated with ascities, portal hypertension or mild hepatic insufficiency (Fig. 5).[101 137 291 302 322 460] Histologically, cirrhosis, determined particularly by the presence of hepatocellular necrosis, fatty infiltration, alcoholic-hyaline (Mallory) bodies in the hepatic cell, stasis of bile and infiltration with polymorphonuclear leukocytes may be present in the liver regardless of hepatic coma. The brain and central nervous system have been studied in patients with cirrhosis who have died in hepatic coma and no specific lesion has been demonstrated conclusively. Perivascular demyelination, endothelial proliferation, increased number and size of protoplasmic astrocytes, meningeal edema, focal hemorrhages and congestion of blood vessels are nonspecific neuropathological findings in the brain [1 21,302 642] No specific lesion has been noted in the kidney of patients who have died in hepatic coma Intercapillary glomerulonephritis, chronic passive congestion, "lower nephron nephrosis," bile nephrosis and acute glomerulonephritis may be associated with cirrhosis [302 351 445]

CLINICAL MANIFESTATIONS

The syndrome of hepatic coma is characterized by various mental and neurological manifestations, which may be fluctuating, regressive, progressive, gradual or rapid Usually, the stages of hepatic coma are classified into impending hepatic coma and deep coma. The mental characteristics of impending hepatic coma are restlessness, poor judgment, euphoria, confusion, depression, lethargy, noisiness, inappropriate behavior, agitation, disorientation, hallucinations and paranoid ideas. The neurological findings may be rigidity, decreased sensory response and characteristically and consistently involuntary movements or tremor. These features are described in the classical report by Adams and Foley. The "flapping" tremor is particularly suggestive of hepatic coma, though it may be found infrequently in other conditions such as uremia, hy-

pokaliemia, ammonia intoxication and polycythemia vera with congestive heart failure.[3,53,137,138,216] This tremor may be observed in the extremities and facial muscles and may be identified by observing the patient with arms outstretched and fingers spread at which time rapid, irregular extension flexion movements at the wrist, elbow, or shoulder occur. Fetor hepaticus and the "flapping" tremor are two of the most ominous clinical features in patients with severe hepatic insufficiency

Another important feature of impending hepatic coma is the invariably abnormal though nonspecific electroencephalographic pattern [1,50,200,390-393,561,597] This consists of various stages as the depth of hepatic coma increases· (1) theta stage, with diffuse waves of a frequency of 4 to 7/second; (2) triphasic stage, characterized by diffuse bilaterally synchronous triphasic waves whose maximal deflection is surface positive; and (3) delta stage with random arrhythmic waves and little bilateral synchrony (Fig 5) [50] No definite relationship between the concentration of blood ammonia and the abnormal electroencephalographic pattern has been established in patients with hepatic coma. The theta stage occurs during impending hepatic coma and also is observed during epileptic seizures, whereas the triphasic and delta stages are present during hepatic coma

The patient in impending hepatic coma may recover spontaneously, have stages of remissions and relapses, remain in a coma for days or several weeks, or unalterably progress slowly or rapidly to death Butt has observed an unusual case of a patient in deep hepatic coma for as long as twelve days with spontaneous recovery [85] Once coma supervenes, the clinical picture is that of a deep quiet sleep, fever, dehydration, slow, deep, prolonged respirations, rapid, irregular pulse and normal arterial blood and cerebrospinal fluid pressures The arterial blood pressure, however may fall and may produce further hepatic, cerebral and renal anoxia [136,359,432] So-called and ill-named hepato-renal syndrome may result as a consequence of the aforementioned renal lesions associated with hepatic disease or arterial hypotension and may manifest itself as oliguria, anuria and azotemia. The neurological signs observed in patients with hepatic coma may be bouts of muscular rigidity or flaccidity,

organs of the body. This would appear to indicate that hepatic coma results from a metabolic abnormality rather than from a specific lesion in the liver, brain or kidney. The morphological manifestations of any type of cirrhosis in a patient who has died from hepatic coma do not differ from those demonstrated when cirrhosis is latent or associated with ascities, portal hypertension or mild hepatic insufficiency (Fig. 5).[101,137,291,302,322,460] Histologically, cirrhosis, *determined particularly by the presence of hepatocellular necrosis*, fatty infiltration, alcoholic-hyaline (Mallory) bodies in the hepatic cell, stasis of bile and infiltration with polymorphonuclear leukocytes may be present in the liver regardless of hepatic coma. The brain and central nervous system have been studied in patients with cirrhosis who have died in hepatic coma and no specific lesion has been demonstrated conclusively. Perivascular demyelination, endothelial proliferation, increased number and size of protoplasmic astrocytes, meningeal edema, focal hemorrhages and congestion of blood vessels are nonspecific neuropathological findings in the brain.[1,21,302,642] No specific lesion has been noted in the kidney of patients who have died in hepatic coma. Intercapillary glomerulonephritis, chronic passive congestion, "lower nephron nephrosis," bile nephrosis and acute glomerulonephritis may be associated with cirrhosis.[302,351,445]

CLINICAL MANIFESTATIONS

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average being a week. The depth of coma may fluctuate from time to time. It has been observed that the longer hepatic coma persists, the poorer the prognosis.

LABORATORY MANIFESTATIONS

There are no significant laboratory tests or tests of hepatic function that are diagnostic or prognostic of hepatic coma or distinguish impending from deep hepatic coma. No consistent differences in the conventional hepatic function tests are present in patients with hepatic disease before and during hepatic coma.[101 201 423] Polymorphonuclear leukocytosis is often observed and may reflect marked hepatocellular necrosis. An increase in the blood urea

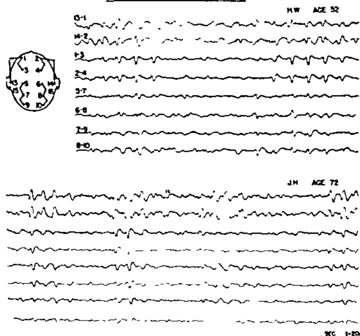
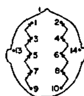
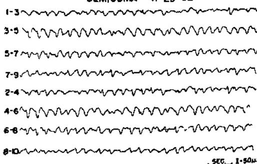


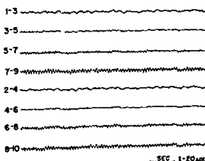
FIG 5 Electroencephalograms of a patient in hepatic coma Under 'alert' is a piece of normal record for comparison (Courtesy Bickford and Butt—J Clin Investigation—June, 1955)

diminished or absent or hyperactive reflexes, absence of corneal reflexes, positive Babinski and Hoffman signs, ankle clonus, grasping and sucking reflexes, response to painful stimuli by shouting, crying or moaning, depending upon the depth of coma and convulsive seizures. Patients in hepatic coma may linger on for days or weeks. Resolution of hepatic coma may occur, but usually death occurs suddenly or unexpectedly as the result of shock, renal insufficiency, fever, electrolyte abnormalities, gastrointestinal hemorrhage, paralytic ileus, bronchopneumonia, bacteremia, abdominal paracentesis or intoxication from sedatives, narcotics, parenteral protein or diuretic agents. The duration of hepatic coma in those patients who die varies from several hours to four weeks the

CHANGES IN EEG WITH DEPTH OF HEPATIC COMA







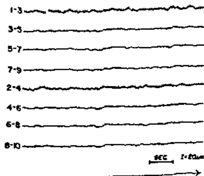


TABLE XIV

SERIAL DETERMINATIONS OF HEPATIC AND ELECTROLYTE TESTS IN A PATIENT WITH POSTNECROTIC CIRRHOSIS AND HEPATIC COMA

Blood	*Normal Values*	*1*	*6*	*10*	*14*	*17*	*20*	*25*	*27*	*30*
Sodium, mEq/l	131–150	131.3	138.9	112.3	141.7	150	112.3	148.6	139.7	135.9
Potassium, mEq/l	4.1–5.6	8.6	2.3	2.9	2.9	2.9	2.6	4.0	5.3	5.5
CO_2, mEq/l	25–28	15	32	33	34	31	33	21	25	21
Chloride, mEq/l	100–108	112.1	94.7	95.2	100.5	105.3	95.2	80.2	81	86.2
Urea Nitrogen, mg/100 cc	8–15	6	15	19	17	16	21	52	86	80.2
Nonprotein Nitrogen, mg/100 cc	25–40	15	20	38	35	37	36	—	95	155
Creatinine, mg/100 cc	0.7–1.3	1.5	1.4	1.4	1.4	1.4	1.6	—	5.5	18.7
Bilirubin, direct/total, mg/100 cc	0.2/1.0	17.6/32.8	15.7/30.8	20.1/32.0	32.8/58.4	29.6/52.8	29.6/53.0	28.8/48.1	30.5/50.3	31.2/48.4
Cephalin cholesterol, units, 48 hr	0–1+	4+	4+	4+	3+	3+	3+	2+	2+	2+
flocculation									—	3.4
Thymol turbidity, units	0–7	4.0	1.9	1.9	5.0	—	4.6	3.2		
Zinc sulfate turbidity, units	3.5–10.5	3.1	2.7	1.4	4.0	—	3.5	2.2	—	2.4
Alkaline phosphatase, Bodansky units	1.5–4.5	6.1	6.7	2.4	4.4	—	—	3.4	—	4.9
Albumin/globulin, gm/100 cc	3.0–4.5 / 2.0–3.5	2.1/1.8	2.1/1.6	2.4/1.5	2.3/1.8	2.3/1.8	2.5/1.6	2.3/1.8	—	1.8/2.1
Ammonia 0.5–2.5γ/100 cc		6.5	8.2	11.1	5.2	6.5	6.6	7.2	7.6	10.9
Urinary output cc/24 hr	—	2940	1850	1268	2650	2006	1550	315	230	155
Fluid intake cc/24 hr	—	1350	4620	4014	3611	1017	3570	3976	1475	1015

Treatment

Days 1–10:
- ← 60 units ACTH/day →
- ← tetracycline 1.0 gm/day
- ← IV fluids + electrolyte replacement
- ← 40 gm Sodium Glutamate/day
- ← *1200–1500 Calories in form of glucose* →
- ← Therapeutic vitamins daily
- ← Oxygen tent →

Days 20–30:
- ← 200–300 mg Hydrocortisone daily →
- ← 20–40 gm Protein / No Protein Supplements →
- ← *Oxygen Tent* →

nitrogen is a common biochemical finding and may be related to renal insufficiency, gastrointestinal bleeding, and assimilation of protein Occasionally, the blood urea is abnormally low indicative of impaired deamination by the diseased liver. The level of blood urea nitrogen may vary in hepatic coma depending particularly on hepatic and renal insufficiency It has been demonstrated that the level of blood ammonia is low in renal insufficiency, and therefore is a more reliable index than the blood ammonia nitrogen in hepatic coma which is often associated with renal insufficiency Concentrations of alpha-amino nitrogen, phenol, lactic acid, pyruvic acid, ammonia and glutamine in the blood may be elevated in patients with hepatic coma, but do not aid in diagnosis Hypoglycemia occurs infrequently in hepatic coma in humans and may augment mental aberration [400, 507] It is considered a pathogenetic factor, however, in hepatic coma in animals as the result of hepatectomy or hepatic necrosis Decreased levels of fasting blood sugar may be observed following a portacaval shunt In this circumstance insulin in the portal blood stream is shunted from the liver and is not metabolized by hepatic insulinase. Decreased levels of cholesterol, phospholipids and, in particular, cholesterol esters, and cholinesterase and elevated values of serum transaminase in the blood are significant biochemical findings in hepatic coma, especially when approaching the time of shunt surgery (Fig 1) (Table XIV)

Abnormalities in acid-base metabolism and electrolyte and water imbalance are particularly common in patients in hepatic coma. Their therapeutic amelioration is at times difficult and frequently perpetuates a vicious cycle of various types of metabolic deficits. Hyponatremia, hypochloremia and hypokaliemia are common biochemical abnormalities, which may be related to hepatocellular damage, sodium restricted diets, ascites, abdominal paracentesis, inanition, vomiting, diarrhea, intestinal intubation, suction, diuresis, intravenous administration of isotonic or hypertonic dextrose, overhydration or use of cation-exchange resins Hyperkaliemia may be present and is usually due to overzealous treatment with potassium salts or to renal insufficiency. Deficits in the concentrations of calcium, phosphorus and magnesium are

output, bowel movements, diet and therapeutic agents together with descriptions of the neuropsychiatric behavior of patients in hepatic coma. It has been found advisable to maintain a chart of the results of various laboratory data listing the hepatic function tests, electrolyte values of the blood and urine, urinalysis, complete blood count, blood urea or nonprotein nitrogen and fluid intake and out put in correct daily chronological arrangement. It may be necessary to insert an indwelling urinary catheter in these patients in order to estimate accurately the urinary output. In this situation, it is recommended that urinary antisepsis be maintained by antibiotics and by irrigations of the catheter with potassium permanganate or some other topical antiseptic agent.

Complete bedrest is advisable in patients in all stages of hepatic coma. In those in impending hepatic coma, sitting up in bed only may be permitted. The physician, however, should use his discretion in allowing patients in impending hepatic coma to have bathroom privileges or sit up in a chair in order to prevent muscular hypotonicity, osteoporosis, joint contractures, decubitus ulcers, venous thrombosis and to maintain the best possible appetite and mental alertness. Nursing personnel should be alerted to change the position of the patient's body to avoid certain complications of bedrest, such as, peripheral venous thrombosis, decubitus ulcers, pneumonitis and orthostatic edema. Siderails are advisable in all these cases, particularly at nighttime. Frequent tapwater enemas instead of hypertonic or saline types are advisable in treating constipation or removing nitrogenous toxic material from the colon. Magnesium salts, hydroxide, sulfate or citrate, have been recommended as the purgative of choice in hepatic coma. It is a method of choice in ridding the colon of ammonium-producing bacteria. High fever is best treated by alcohol sponge baths, icewater enemas, ice-bags or the application of cold packs to the body. Oral and ocular hygiene measures should be resorted to in the form of mouth antiseptics, glycerine applied to the lips and ophthalmic boric acid drops. Intercurrent infections should be managed vigorously by antibiotics. The bacterial organism should be identified by culture and its sensitivity to various antibiotics demonstrated. In any event, providing the patient is not allergic to antibiotics, the administra-

other biochemical abnormalities observed even if renal function is normal Respiratory alkalosis, in which the pH in the plasma is increased, and the carbon dioxide decreased, may be present early in hepatic coma. Its cause is obscure but may be related to ammonia intoxication, hypokaliemia or decreased cerebral oxygen consumption [512, 615, 660] Eventually, metabolic acidosis due to renal insufficiency or respiratory acidosis due to respiratory defect may supervene It is apparent that there is no consistent alteration in the serum electrolytes and pH in patients in hepatic coma, and frequently they are induced iatrogenically

TREATMENT

The therapeutic management of impending or deep hepatic coma involves the most complete, careful and expedient observation and co-operation possible between attending physicians, nurses and laboratory personnel in a manner very similar to the treatment of patients with massive gastrointestinal hemorrhage, diabetic coma, adrenal cortical insufficiency or drug intoxications As previously mentioned in the pathogenesis of hepatic coma, certain preventative measures should be observed in all patients with cirrhosis with or without impending hepatic coma These are, in particular, the conventional treatment of certain coma complications, such as, intercurrent infections, drug intoxications with arsenic, phosphorus, copper, carbon tetrachloride, barbiturates or narcotics, gastrointestinal hemorrhage, alcoholism, diabetes mellitus such as commonly observed in patients with hemochromatosis, subdural hematoma frequently present in alcoholics, metastatic cerebral hepatoma or cholangioma and the correction of electrolyte and fluid imbalance observed following diuresis or abdominal paracentesis Because of the high mortality observed in patients with hepatic coma, it behooves the attending medical personnel to facilitate rapidly the exact therapeutic measures of these complications of cirrhosis. One of the most important of these principles is the arrest of gastrointestinal hemorrhage which perpetuates hepatic anoxia and elevated blood ammonia

It is necessary to maintain an accurate record of body temperature, pulse, arterial blood pressure, respirations, fluid intake and

The intake of protein may be gradually increased to 50 gm daily only if recovery is apparent If relapse occurs, further restriction of dietary protein is necessary. Absolute restriction of protein is recommended by the dietary treatment of patients in hepatic coma This may be accomplished by tube feedings of hypertonic glucose and fat emulsion and by hypertonic solutions of glucose administered intravenously Hyperalimentation of hypertonic glucose and fat emulsion may provoke vomiting, diarrhea and paralytic ileus with further embarrassment to the already present eletrolyte and water deficit, on the other hand, hypertonic glucose administered intravenously and usually containing electrolytes and multivitamins, may induce thrombophlebitis, pyogenic reactions, cellulitis and water-logging. Three thousand cubic centimeters of 10 per cent dextrose administered daily will afford the patient 1,200 calories and an additional 1,000 calories may be supplied by hypertonic glucose, grape juice or peanut oil introduced by gastric lavage Lipomul® (Upjohn) is an emulsion containing 10 per cent fat and 10 per cent glucose Three hundred cubic centimeters administered by gastric tube will afford the patient 1,200 calories (4 calories/cc), but the amount administered should be regulated carefully in order to prevent gastrointestinal intolerance.[494]

The physician encounters a delicate therapeutic balance in the administration of protein to patients with severe hepatic insufficiency. Inadequate amounts of protein retard hepatocellular healing while excessive amounts may precipitate hepatic coma Therefore, the dietary management of these patients is highly individualized and at best it is wise to administer the patient at least 1 gm. of protein/kilogram of body weight as soon as possible The physician treating patients with chronic liver disease is forced with the therapeutic problem of "calories vs protein." Protein should be eliminated from the diets of patients with hepatic coma for the shortest time possible On the other hand, it may be advisable to maintain cirrhotics with amounts of protein less than 70 to 100 gm daily Butt noted two demented patients who were found to have cirrhosis in which restriction of dietary protein was ameliorative [85] The administration of dietary protein to the cirrhotic patient also becomes a problem when anorexia, malnutrition, need for restriction of

tion of depot procaine-pencillin with dihydrostreptomycin or intramuscular tetracyline or one of the broad-spectrum antibiotics is recommended in the routine management of patients in hepatic coma because of their susceptibility to infection. Oxygen should be prescribed to the patient in the amount of 8 liters/hour by tent to lessen the possibility of cerebral or hepatic hypoxia. Ascites has been recognized to interfere with respiration and reduce the vital capacity of the lungs Careful administration of oxygen should be watched to prevent "oxygen poisoning" in patients with respiratory acidosis, particularly in those patients with pulmonary emphysema An open respiratory air-way should be maintained in comatose patients, in whom collections of nasopharyngeal and bronchial secretions may obstruct the upper respiratory system. Intestinal decompression by long intestinal intubation is advisable in the management of paralytic ileus observed not uncommonly in patients in hepatic coma Arterial blood pressure should be maintained by the careful administration of transfusions of blood or plasma-expanding agents, or Vasoxyl®, Levophed® or Neo-synephrine® It is apparent that the overzealous use of transfusions of blood has inherent dangers in these patients, particularly in their content of protein and that the abuse of vasoconstrictor drugs to maintain intractable arterial hypotension can induce hepatic and renal anoxia [69-71,76,149,156,323,432] The intramuscular administration of an iron-dextran complex (Imferon®) should be considered in the treatment of iron-deficiency anemia in patients with hepatic coma.[20,98,671] Sedative and hypnotic drugs are necessary to control restlessness, euphoria, abnormal behavior and convulsive seizures and analgesics and narcotics to diminish abdominal pain It is advisable that small doses of phenobarbital or demerol be employed discriminately for these purposes

Strict attention should be paid to the selection of a proper diet in the management of patients in hepatic coma. If possible, it is advisable to prescribe a diet containing from 1,800 to 2,400 calories, 20 gm of protein, 300 to 400 gm. of carbohydrate, sufficient in fat for palatability to patients in impending hepatic coma This may be accomplished by oral or tube feedings and may be supplemented by the intravenous administration of 10 per cent glucose in water.

chills. Fat emulsions tend to produce abnormalities in hepatic function tests, which tend to return to the preinfusion state after emulsions are withdrawn.[220,452] Abuse of intravenous administration of glucose may be demonstrated in electrolytic deficits, particularly hyponatremia, hypokaliemia, overhydration, pulmonary edema and even the precipitation of hepatic coma and death. It is customary to prescribe unreasonably large doses of vitamins parenterally to patients in hepatic coma, most of which are excreted soon in the urine. There is no actual benefit to these patients, and their costliness becomes readily apparent. It is discomforting for the medical consultant to find a turbid, highly colored, hypertonic intravenous solution containing exorbitant amounts of vitamins and minerals being administered unnecessarily to a patient in hepatic coma. The fact that the majority of these patients have no evidence of avitaminosis suggests large therapeutic doses of vitamins unreasonable. Actually, the dosage contained in two standard therapeutic vitamin preparations in addition to no more than 5 mg of vitamin K and possibly 1 mcg of vitamin B_{12} should be considered adequate.

As alluded to earlier, treatment of patients in hepatic coma should also be directed toward maintaining electrolyte and water balances. Daily attention should be paid to the patient's fluid balance. Dehydration or overhydration may be determined by accurate measurement of the patient's intake and output of fluid and the hematocrit. Excessive intake of fluid in the presence of oliguria or anuria may induce pulmonary edema and death, and in the presence of normal renal function may lead to hyponatremia, anasarca and water intoxication. Failure to correct dehydration, on the other hand, induces oliguria and hemocentration. Patients with severe hepatic disease have been shown to have a decreased tolerance to water.[137,140]

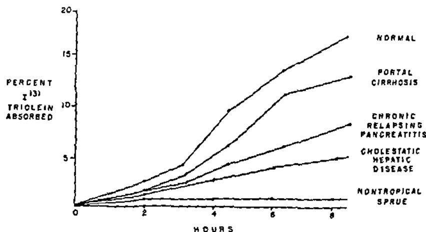
Exclusive of therapy with glucose and vitamins, other suggested types of specific treatment of hepatic coma are antibiotics, adrenocorticotropic hormone, adrenal steroids, glutamic acid, thioctic acid and arginine. The broad spectrum antibiotics have been employed therapeutically because of their beneficial use in the management of acute fulminent hepatitis, protection against infections and

sodium and gastrointestinal symptoms such as nausea, vomiting, intolerance to fatty foods, constipation, diarrhea and abdominal distention are present. Systematic management of these problems, parenteral hyperalimentation and close co-operation with the dietician, who is often able to select appetizing and colorful diets, may be rewarding. Occasionally, salt-poor serum albumin in the amount of 25 to 50 gm per day may benefit patients in hepatic coma, particularly when marked hypoalbuminemia, ascites or edema is present, usually it is ineffective, not without inherent danger and costly.

One of the most highly respected types of therapy employed in patients with hepatic coma is the parenteral administration of glucose and vitamins. Frequently the benefit derived from this is dramatic in patients with impending hepatic coma or early in the course of deep hepatic coma. Enthusiastic results have been reported by the continuous intravenous administration of 3,000 to 4,000 cc of 10 per cent glucose containing 50 to 100 mg of thiamine and 250 to 500 mg of nicotinic acid.[137,139,276,293,302,574] Experimental protection of the diseased liver by glucose, the presence of hypoglycemia in the experimental hepatectomized animal, the neutralization of ammonia by glutamine, breakdown of the Krebs cycle and cocarboxylase enzymatic systems in advanced hepatic disease, the elevation of lactic acid and pyruvic acid in the blood of patients in hepatic coma and the therapeutic use of thiamine and nicotinic acid in delirium tremens and various encephalopathies have prompted combined glucose-vitamin treatment in hepatic coma[11,273,293,314,321,442,446,511,515,549a,574] Summerskill has employed hypertonic Dexin®, a partially hydrolyzed starch by gastric tube or intravenously using a polyethylene catheter[137,139,594] This substance (1 gm. equivalent to 4 calories) may satisfy the recommended intake of 2,000 calories daily without overhydration. Fat emulsions administered intravenously largely supply the caloric requirements in hepatic coma[4,67,220,329,462,612] Supplying 1,200 cc of Lipomul®, which contains 15 per cent peanut oil and 4 per cent glucose, affords 1,800 calories The solution can be infused for reasonable periods of time without causing any phlebitis, but may induce an occasional case of fever, nausea, anorexia, vomiting, dizziness and

has been unpredictable (Table XII). In fact, steroid therapy may render false clinical improvement, reduction in hyperbilirubinemia, but without improvement in hepatocellular necrosis. Massive doses of cortisone, 250 mg every 6 hours, has been reported to produce temporary alertness and activity, and improve oral nourishment in patients in hepatic coma.[451] The use of these hormones in patients with cirrhosis and hepatic coma usually is a "desperation measure" and may induce serious complications, such as retention of fluid, acute pancreatitis, gastrointestinal hemorrhage, venous thrombosis and electrolyte imbalances and masked infection.[63 64 102 262 279 347 542 553 637 670 658 693]

The therapeutic results of intravenous administration of large doses of glutamic acid or sodium glutamate (Glutavene®) as a specific treatment of hepatic coma have been arbitrary and conflicting (Table XIV).[85 137 222 390 393 510 512 543 549 562 564 634 656] Glutamic acid therapy has been employed in these cases because the mechanism of hepatic coma has been considered due to or similar to ammonia intoxication. This drug has been found by some observers to decrease the high content of ammonia in the blood in patients with hepatic coma or in coma due to ammonium chloride, proteins or following a portacaval shunt in patients with cirrhosis.[82 171 214 216 390 393 460 510 512 549 566 587 616 634 656] The fact that the mechanism of hepatic coma in patients with cirrhosis has not been proved to be ammonium intoxication has made many skeptical of this type of therapy. It has been concluded that glutamic acid therapy is specific for cases of exogenous or ammoniagenic hepatic coma. That the therapeutic results are unimpressive in endogenous hepatic coma may be seen in poor results observed in 200 cases reported by McDermott.[390,393] Bessman regards glutamic acid therapy in this condition as a binding rather than specific form of treatment.[46 47] The drug is administered intravenously in average doses of 40 gm. daily and, when prescribed as the sodium salt, introduces large amounts of this cation into the blood of the patient with cirrhosis (Table XV). Some observers have considered doses up to 200 or more gm. administered within thirty-six to forty-eight hours to be more effective.[512] The occasional dramatic response to glutamic acid therapy in a patient with cirrhosis probably merits its use until



AVERAGE I^{131} ABSORPTION CURVES IN VARIOUS CONDITIONS

Fig 6

reduction of intestinal bacteria in an effort to decrease the amount of enterogenous ammonia.[137,187,227,249] The administration of a broad-spectrum antibiotic such as Neomycin® or chlortetracyline, from 1-3 gm. daily, orally, intramuscularly or by nasogastric tube, will reduce the intestinal bacterial flora that produce ammonium, thereby lowering the concentration of ammonium in the blood, but it will also promote decreased bodily weight, negative nitrogen balance, increased urinary nitrogen and possibly increased fecal nitrogen.[143,188,215,383] The dangers of broad-spectrum antibiotics in the treatment of hepatic coma are demonstrated by numerous reports of therapeutic failures and evidences of hepatic toxicity, negative nitrogen balance, fatty infiltration of the liver, avitaminosis K, pseudomembranous enterocolitis, gastrointestinal hemorrhage and vomiting. Reduction of nitrogenous wastes in the colon in order to reduce blood ammonia should be an important therapeutic measure. This may be accomplished by enemas or intestinal sterilization employing the broad-spectrum antibiotics.[194,195] Neomycin® or tetracycline are prescribed in doses of 2 to 4 gm daily for intestinal sterilization

The use of adrenocorticotropic hormone or corticosteroids in the management of patients with cirrhosis who are in hepatic coma

a better agent is discovered. Generally, glutamic acid therapy has been found to be more efficacious in hepatic coma resulting from or following the administration of dietary protein or ammonium salts, surgical shunt procedures, infections, or gastrointestinal hemorrhage, so-called "complicated" hepatic coma On the other hand, in hepatic coma without these complications, but in which there is progressive or marked hepatocellular damage, this therapy appears useless.

Thioctic acid has been employed in the treatment of hepatic coma with unimpressive results which, to date require further confirmation [594, 604] Thioctic acid, lipoic acid or the pyruvate oxidation factor, a biocatalyst, has an essential role in the oxidation of alpha-keto acids and in the transference of pyruvic acid into the Kreb cycle. L-arginine, which is also active in the hepatic Krebs cycle, has been demonstrated to reduce elevated blood ammonia levels in hepatic coma [47, 194, 185, 190] These newer types of therapy require further investigation to be considered effective in the treatment of hepatic coma The intravenous administration consists of 25 gm. of arginine hydrochloride with 50 gm of glucose in 500 cc of water, or one of the newer commercial preparations of the glutamic acid salt of arginine every six hours Acidosis may be produced by arginine, and hypernatremia and alkalosis from sodium glutamate. The mechanism in which arginine produces lowering of the blood ammonia is different from that of glutamic acid which is related to the ornithine cycle. It would seem that, in evaluating the therapeutic results of glutamic acid, corticosteroids, arginine and thioctic acid, these must be considered in light of proper therapeutic controls One should be cautioned against an overzealous therapeutic attitude because glucose, fluids, oxygen, antibiotics and transfusions of blood are often not considered when evaluating the results of newer types of therapy in hepatic coma

PROGNOSIS AND SURVIVAL

The prognosis of hepatic coma in patients with cirrhosis is generally poor Spontaneous recovery from hepatic coma is not unusual and ofttimes a specific type of therapy is incorrectly credited [85, 221, 397, 574] The prognosis is favorable, for example, in

TABLE XV

DAILY LABORATORY DATA FROM A PATIENT WITH PORTAL CIRRHOSIS IN HEPATIC COMA

	Normal	1	7	16	24	31	44	71
Serum bilirubin, direct/total mg per 100 cc	0.2 / 1.0	6.0 / 9.3	10.5 / 19.1	11.2 / 20.4	10.0 / 17.7	3.7 / 6.4	2.9 / 5.3	0.6 / 1.1
Serum albumin/globulin gm per 100 cc	3.5 / 2.5	2.6 / 3.1	2.4 / 4.3		2.6 / 4.0	2.5 / 3.1	3.0 / 2.9	3.1 / 2.4
Blood urea nitrogen mg per 100 cc	8 15	7	10	12	15		12	12
Cephalin cholesterol flocculation, 24 hr	0, 1+	2+	3+		3+	3+	3+	2+
Thymol turbidity, units	0 7	26.1	25.8					
Zinc sulfate turbidity, units	3.5 10 5	21.7	27.8		23.2	18.6	17.2	11.0
Alkaline phosphatase, Bodansky units	1.5 4	5.1	6	3.7	25.4	13.7	17.9	15.5
Bromsulfalein, % retention in 45 min	0 5							
Blood Ammonia γg per 100 cc	0 05 0 35	4	6	8	7	4	1.6	37 / 0.3
		← Hepatic Coma →					Survival	

Daily Treatment consisted of 2400 calories (3000 cc 10% glucose IV and 300 gm glucose by gastric tube, 40 gm sodium glutamate IV, multivitamins, oxygen tent, and prednisone (10th to 28th day)

those cases in which infection, dietary protein, slight gastrointestinal hemorrhage or electrolyte imbalance is responsible, and poor in prolonged cases of treated hepatic coma. It has been suggested that the incidence of recovery in patients with nutritional or alcoholic portal cirrhosis in hepatic coma is better than those with other types of cirrhosis. This is commonly demonstrated in patients with postnecrotic cirrhosis in which case restoration of hepatocellular damage is lacking Generally, not more than 10 to 20 per cent of patients with all types of cirrhosis may recover from hepatic coma despite any type of therapy (Table XVI).

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TABLE XVI
THERAPEUTIC RESULTS IN PATIENTS WITH CIRRHOSIS AND HEPATIC COMA

	Diagnosis Cirrhosis	*Complications*	*Hepatic Coma Impending (IHC) Deep (DHC)*	*Duration Days*	*Specific Treatment*	*Result*
1	Portal	Ascites	DHC	11	Na Glutamate	Death
2	Postnecrotic	Esophageal Hemorrhage	DHC	6	Na Glutamate	Death
3	Postnecrotic	Hemorrhage	DHC	3	Na Glutamate	Death
4	Postnecrotic	Pregnancy Protein Feeding	DHC	30 (Temporary Awakening)	Na Glutamate & ACTH	Death
5	Portal	Infection	IHC → DHC	27	Conventional	Death
6	Portal	Ascites	IHC	17	Conventional	Survival
7	Primary Biliary	Esophageal Hemorrhage	IHC → DHC	11	Blood Transfusions	Death
8	Portal, Post-hepatic	Hyponatremia	IHC → DHC	17	Na Glutamate ACTH	Death
9	Portal	Esophageal Hemorrhage	IHC	4	Blood Transfusions	Survival
10	Portal	None	DHC	7	Na Glutamate	Death
11	Hemochromatosis	Ascites Alcoholism	DHC	18	Na Glutamate	Death
12	Portal	Gastroenterostomy	DHC	9	Na Glutamate	Death
13	Portal	Malnutrition	IHC	5	Na Glutamate	Survival
14	Postnecrotic	Anasarca	DHC	17	Na Glutamate	Death
15	Portal	Portacaval Shunt	IHC	5	Na Glutamate	Survival
16	Portal	Hepatic Artery Ligation	DHC	12	Na Glutamate Antibiotics	Death
17	Portal	Alcoholism	DHC	2	Conventional	Death
18	Portal	Phosphorus (Suicide)	DHC	14	Arginine	Death
19	Portal	Esophageal Hemorrhage	IHC⇄DHC	97	Arginine 250 800 units ACTH or Dexomethasone 0 03 gm daily	Death

those cases in which infection, dietary protein, slight gastrointestinal hemorrhage or electrolyte imbalance is responsible, and poor in prolonged cases of treated hepatic coma. It has been suggested that the incidence of recovery in patients with nutritional or alcoholic portal cirrhosis in hepatic coma is better than those with other types of cirrhosis. This is commonly demonstrated in patients with post-necrotic cirrhosis in which case restoration of hepatocellular damage is lacking. Generally, not more than 10 to 20 per cent of patients with all types of cirrhosis may recover from hepatic coma despite any type of therapy (Table XVI)

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constituents in every respect (protein, fat, carbohydrate, calories, minerals, vitamins and water) necessary for optimal body-building and functioning, as recommended by the Food and Nutrition Board of the National Research Council [2,7,11,13,18,19]

APPROXIMATE COMPOSITION

Calories	2 600	
Protein	100	gm
Fat	120	gm
Carbohydrate	300	gm
Calcium	1 094	gm
Iron	14 80	mg
Phosphorus	1 612	gm
Vitamin A	10 054	I U
Thiamin	1 591	mg
Riboflavin	2 102	mg
Niacin	16 21	mg
Ascorbic Acid	119	mg

DAILY FOOD PATTERN

1 Leafy green and yellow vegetables — 1 or more servings
2 Citrus fruit and other foods high in ascorbic acid — 1 or more servings
3 Potatoes and other vegetables and fruit — 2 or more servings
4 Milk — 2 or more cups
5 Meat poultry fish — 1 serving
Eggs — 4 or more a week or dried beans, peas nuts peanut butter or more meat when eggs are not used
6 Bread, flour and cereals (whole grain, enriched) — 1 or more servings
7 Butter or fortified margarine — some daily

SAMPLE MENU

Breakfast	*Dinner*	*Supper*
Orange Juice	Roast Beef au Jus	Consommé
Oatmeal	Whipped Potatoes	Chicken à la King
Scrambled Eggs	Parsleyed Carrots	Buttered Rice
Bacon	Fresh Fruit Salad	Buttered String Beans
Toast	Devil's Food Cake	Sliced Tomato Salad
Butter	Milk	Jello Cubes with Whipped Cream
Coffee	Bread	Milk
Cream	Butter	Bread
Sugar		Butter
		Crackers

Chapter 17

DIETARY MANAGEMENT OF CIRRHOSIS

INTRODUCTION

THE THERAPEUTIC use of various diets constitutes one of the major roles in the management of cirrhosis and its complications. In order to understand clearly the composition of these diets, it is advisable to become acquainted with a nutritious general diet employed uniformly in hospitals throughout this country. This diet serves as a guide in the selection and preparation of more specific diets. It is designed for maintaining normal nutrition in healthy individuals in the United States. Because a recommended amount of calories varies with the patient's age, sex, and activity, it is necessary to adjust the patient's daily caloric intake.

GENERAL DIET

The general diet is planned to teach by example the patients good nutrition. It contains sufficient amounts of the essential food

APPROXIMATE DAILY REQUIREMENT OF FOOD CONSTITUENTS NEEDED FOR OPTIMAL BODY BUILDING AND FUNCTIONING[4,16]

	Adult		Child	
Calories (per kg)	Basal	25	Under 1 year	95-100
	Bed rest	27	1-2 years	90-100
	Very light exercise	30-35	2-5 years	80-90
	Light exercise	35-40	6-9 years	70-80
	Moderate exercise	40-45	10-12 years	60-75
	Hard labor	45-50	14-17 years	50-65
	Very severe labor	50-60		
Protein	2 3–1½ gm/kg of body weight or 10-15% of the total calories		Under 1 year—4 gm/kg. Over 1 year 2.3 gm/kg of body weight or 15% of the total calories	
Fat	1-2 gm/kg of body weight or 30-40% of the total calories		2-3 gm/kg of body weight or 35% of the total calories	
Carbohydrate	4-6 gm/kg of body weight or 50-60% of the total calories		6-10 gm/kg of body weight or 50% of the total calories	

fat, on the other hand, in the treatment of disease of the liver in humans is probably needless and unnecessary. This diet in all probability contains calories and amounts of protein, carbohydrate and fat in excess of those absolutely necessary for the treatment of diseases of the liver.[3,7,8,11,14,19] When normal body weight is regained and malnutrition cured, it is then advisable to prescribe a general diet for these patients. An adequate amount of vitamins, minerals, methionine and choline is supplied in this diet.

APPROXIMATE COMPOSITION

Calories	3,460
Protein	150 gm
Carbohydrate	400 gm
Fat	140 gm
Calcium	2.7 gm
Iron	20 mg
Phosphorus	2.8 mg
Vitamin A	12,500 units
Thiamine	2.3 mg
Riboflavin	4.8 mg
Niacin	21 mg
Ascorbic acid	150 mg

SAMPLE MENU

Breakfast	
Fruit Juice or Fruit with sugar	1 large serving (See Lists 1 and 3)
Cereal	1 serving (See List 4)
Eggs	2
Bacon or other breakfast meat	as desired
Bread or Toast	2 slices
Butter	as desired
Jelly	1 tablespoon
Milk	1 cup
Coffee or Tea	as desired
Sugar	2 tablespoons
10 A.M.	
Fruit Juice or Fruit with sugar	1 large serving (See Lists 1 and 3)
Noon Meal	
Meat, Fish, or Poultry	4 ounces (See List 5)
Potato or Substitute	1 serving (See List 4)
Vegetable	1 serving (See List 2)
Salad (fruit or vegetable)	1 serving (See Lists 2 and 3)
Dessert	1 large serving (See List 3)
Bread	1 slice

STANDARD DIET FOR PATIENTS WITH DISEASES OF THE LIVER

The use of this diet is directed toward supplying a high number of calories, increased amounts of protein and carbohydrate and a low content of fat compatible with palatability to patients with hepatic disease It has been shown that severe dietary restriction of

FOODS INCLUDED AND EXCLUDED IN DIETARY PROGRAM FOR LIVER DISEASE

Type of Food	*Foods Included*	*Foods Excluded*
Beverage	Carbonated beverage, coffee, tea, milk drinks, milk at least five cups daily.	Alcoholic
Bread	Any with emphasis on whole grain or enriched	None
Cereal	Any with emphasis on whole grain or enriched	None
Dessert	Cakes, cookies, custard, gelatin ice cream, sherbets	Use desserts high in fat in moderation
Fat	Butter, fortified margarine, salad dressing, salad oil or shortening Avoid excessive fats	Use in moderation
Fruit	Any	None
Meat egg or cheese	Any meat, fish, fowl or cheese except those listed under Foods Excluded, at least 10 ounces daily; eggs, at least 2 daily	None
Potato or substitute	Potato, hominy, macaroni, noodles, rice, spaghetti	None
Soup	Any from "Foods Included"	Any other
Sweets	Candy, honey, jam, jelly, molasses, syrup, sugar	Excessive chocolate
Vegetable	Any	None
Miscellaneous	Gravy, olives in moderation, pickles, relishes, spices in moderation, vinegar, white sauce, nuts	

Meat Exchanges—List 5

Meat and Poultry (beef, lamb, pork, liver, chicken, turkey, sweetbreads, 4 ounces or more	Egg—4
Fish—4 ounces or more	Cheese, cheddar type—4 ounces
Salmon, tuna, crab, lobster—1 cup	Cottage Cheese—1 cup
Shrimp, clams, oysters—20 small	Peanut Butter—8 tablespoons
Sardines—12 medium	Cold Cuts (4½"x⅛") any kind—4 slices
	Frankfurters—4

Fat Exchanges — List 6 (May be used as desired)

Bacon	French Dressing
Butter or Margarine	Mayonnaise
Cream, light	Oil or Cooking Fat
Cream, heavy	Nuts
Avocado	Olives
Cream Cheese	

Miscellaneous Exchanges — List 7

Desserts, any kind

Jellies, Jams, Preserves, Honey

INSTRUCTIONS TO PATIENT

Be sure to eat all foods as listed on your meal plan.

Include in between meal nourishments unless they interfere with your appetite for the following meal.

Include additional foods in your diet if desired.

Limit low caloric foods such as broth, tea, coffee, excess roughage or high fiber foods.

It is recommended that you use simply prepared meats and vegetables; however no foods are restricted on this diet.

Use fried or greasy foods in moderation.

Use liberal servings of meat, fish, poultry, milk and milk products, concentrated sweets such as jelly and hard candies.

Keep regular meal hours.

HIGH-PROTEIN, HIGH-CARBOHYDRATE DIET CARBOHYDRATE, 500, PROTEIN, 200; FAT-AD LIB

This High-Protein, High-Carbohydrate Diet is an adequate diet supplemented with foods that are high in protein and carbohydrate content. It is used at the Ochsner Clinic primarily for patients with diseases of the liver who require additional amounts of calories, protein, and carbohydrate beyond that supplied by the standard diet. It has been observed that most patients with hepatic disease find this diet either difficult to ingest completely or to cause postprandial epigastric fullness, nausea and vomiting which

Butter	as desired
Jelly	1 tablespoon
Milk	1 cup
3 P.M.	
Milk	1 cup
Evening Meal	
Meat, Fish, or Poultry	4 ounces (See List 5)
Potato or Substitute	1 serving (See List 4)
Vegetable	1 serving (See List 2)
Salad (vegetable or fruit)	1 serving (See Lists 2 and 3)
Dessert	1 large serving
Bread	1 slice
Butter	as desired
Jelly	1 tablespoon
Milk	1 cup
8 P.M.	
Sandwich – Meat	2 ounces
Bread	2 slices
Fat	as desired
Milk	1 cup

EXCHANGE LIST

Beverage Exchanges – List 1

Milk – whole, buttermilk, or non fat milk. Milk drinks such as eggnog, milk shake, malted milk, milk fortified with powdered non fat milk, Gevral or protenum

Fruit Juices sweetened

Coffee

Tea

Carbonated beverages

Vegetable Exchanges – List 2

Any canned, fresh, or frozen vegetables. One half (½) cup is an average size serving

Fruit Exchanges – List 3

Any canned, frozen or dried fruits, any fresh fruits with added sugar. One half (½) cup is an average size serving

Bread Exchanges – List 4

Bread–1 slice
Biscuit, roll (2" dia.)–1
Muffin (2" dia.)–1
Cornbread (1½")–1
Cereals, cooked–½ cup
Cereals, dry–¾ cup
Rice, grits, spaghetti, noodles, macaroni, cooked–½ cup
Crackers, Graham (2½")–2
Oysters (½ cup)–20
Saltines (2" sq.)–5
Soda (2½" sq.)–3
Flour–2½ tablespoons
Vegetables–Beans and Peas (Limas, navy, split peas, cowpeas) cooked–½ cup
Baked Beans–¼ cup
Corn–⅓ cup
Pop corn–1 cup
Parsnips–⅔ cup
Potatoes, white–1 small or ½ cup
Potatoes, sweet–¼ cup

	Milk	Milk
	Peach Juice	Bread
	Bread	Butter
	Butter	
10:00 A.M.	2:00 P.M.	8:00 P.M.
Chocolate Milk	Protein—Milk Shake	Milk
		Cheese Sandwich

HIGH-CALORIC, HIGH-PROTEIN, SODIUM-RESTRICTED DIET

This diet is used for patients with diseases of the liver and ascites or edema. It provides for increased intake of calories, protein and carbohydrate and a reduced dietary intake of sodium in the amount of approximately 1 gm daily (2.5 gm. NaCl). It is necessary to prepare all foods without salt. Salt substitutes may be employed for seasoning. There are many types, most of which contain potassium chloride, tricalcium phosphate, potassium glutamate in addition to natural flavorings or spices, if preferred (Salt-Ex,® Neocurtasal,® Adolphs, Co-Salt,® Diasal®). The sodium content of these substitutes is approximately 15 mg./100 gm or 0.65 mg. level teaspoon. Sodium-restricted diets should always be supervised by a physician who should be aware of their inherent dangers.[1,5,9,15,17] For detailed information on low-sodium and high-protein diets employed in the management of cirrhosis, the reader is referred to an article by R. M. Kark, "Low Sodium and High Protein Diets in Laennec's Cirrhosis."[9] It is possible to increase the palatability of a sodium restricted diet by the addition of spices, in which the content of sodium is not appreciable.

Approximate Composition

Calories	3,400
Protein	150 gm
Carbohydrate	400 gm
Fat	140 gm
Calcium	2.7 gm
Iron	20 mg
Phosphorus	2.8 mg
Vitamin A	12,500 I.U.
Thiamine	2.3 mg
Riboflavin	4.8 mg
Niacin	21 mg
Ascorbic acid	150 mg
Potassium	5.0 gm (estimated)
Sodium	1.0 gm

further impedes the recommended caloric intake. The question has been raised whether the diseased liver can utilize effectively a diet excessive in calories and protein. There is a lack of evidence also that, in most instances, it is necessary to exceed the dietary composition of even the standard diet in the treatment of diseases of the liver. The fat is kept as low as is compatible with maximum palatability and the diet contains a high-protein content. No foods are prohibited by this diet provided high-protein foods are eaten by the patient. The fat is not limited except to the extent of avoiding excessive ingestion of fried foods, gravies, sauces and rich desserts.

APPROXIMATE COMPOSITION

Calories	4,300	
Protein	200	gm
Fat	170	gm
Carbohydrate	500	gm
Calcium	2 610	gm
Iron	24 10	mg
Phosphorus	3 200	gm
Vitamin A	25,913	I U
Thiamin	2.53	mg
Riboflavin	5 67	mg
Niacin	21 41	mg
Ascorbic acid	189	mg

FOODS ALLOWED

All Foods listed on the Full Diet plus

Large servings of meat, fish, poultry and eggs

Liberal use of milk and milk products

Liberal use of bread and bread products, sweets, fruit juices with sugar

Use of in between meal nourishment, e g , eggnog protein supplement or milkshake feedings, etc

SAMPLE MENU

Breakfast	Dinner	Supper
Large Orange Juice	Cream of Asparagus Soup	Consommé
Oatmeal	Large Serving Roast Beef au Jus	Large Serving Sliced Chicken
2 Scrambled Eggs	Whipped Potatoes	Buttered Rice
2 Strips Bacon	Parslied Carrots	Buttered Beans
2 Slices Toast	Buttered Broccoli	Buttered Yellow Squash
Butter	Fresh Fruit Salad	Sliced Tomato Salad
Coffee	Devil's Food Cake	Jello Cubes with Whipped Cream
Sugar	Ice Cream	Grape Juice
Cream		

	Milk	Milk
	Peach Juice	Bread
	Bread	Butter
	Butter	
10 00 A M	2 00 P M	8 00 P M
Chocolate Milk	Protein—Milk Shake	Milk
		Cheese Sandwich

HIGH-CALORIC, HIGH-PROTEIN, SODIUM-RESTRICTED DIET

This diet is used for patients with diseases of the liver and ascites or edema It provides for increased intake of calories, protein and carbohydrate and a reduced dietary intake of sodium in the amount of approximately 1 gm. daily (2.5 gm NaCl) It is necessary to prepare all foods without salt. Salt substitutes may be employed for seasoning There are many types, most of which contain potassium chloride, tricalcium phosphate, potassium glutamate in addition to natural flavorings or spices, if preferred (Salt-Ex,® Neocurtisal,® Adolphs, Co-Salt,® Diasal®) The sodium content of these substitutes is approximately 15 mg /100 gm or 0 65 mg level teaspoon Sodium-restricted diets should always be supervised by a physician who should be aware of their inherent dangers [1,5,8,15,17] For detailed information on low-sodium and high-protein diets employed in the management of cirrhosis, the reader is re[illegible] to an article by R M Kark, "Low Sodium and High Protein [illegible]"[9] It is possible to increase the palat[illegible] [illegible] spices, in which the content of sodium [illegible]

Approximate Composition	
Calories	3,400
Protein	150 gm
Carbohydrate	400 gm
Fat	130 gm
Calcium	2 7 gm
Iron	20 mg
Phosphorus	2 8 mg
Vitamin A	12,500 I U
Thiamine	2 3 mg
Riboflavin	4 8 mg
Niacin	21 mg
Ascorbic acid	150 mg
Potassium	5 0 gm (estimated)
Sodium	1 0 gm

T		
Beverage.	Milk or buttermilk (4 cups daily), one with 2 tablespoons low-sodium protein supplement, tea; coffee, carbonated beverage.	Alcoholic
Bread	Unsalted bread	Bread or crackers made with baking powder, soda or salt
Cereals	Cooked cereals prepared without salt, puffed rice, puffed wheat, shredded wheat	Dry prepared cereals except those listed under 'Foods Included"
Dessert	Custard or ice cream made from milk allowance, gelatin desserts made with plain gelatin and foods allowed, unsalted fruit pie	Desserts prepared with salt, baking powder, baking soda, or egg white, commercial gelatin desserts, commercial ice cream and Rennet desserts
Fat	Unsalted butter; unsalted cooking oil; salad dressing made without salt celery or garlic salt, unsalted shortening	Bacon fat, salted butter, salt
Fruit	Any fresh frozen or canned fruit, any fruit juice fresh or canned except those in Foods Excluded list	Salted tomato juice or vegetable cocktail juice
Meats Eggs Cheese	Fresh oysters fresh water fish, water packed salmon or tuna, any meat except those listed under Foods Excluded Meats, 10 ounces daily, eggs, 2 daily without salt	Salted, smoked or canned meats, fish or fowl frozen fillet of fish except white fish, pike and lake trout, shell fish except fresh oysters glandular meat except liver and heart, all cheese
Potato or Substitute	Potato, macaroni, noodles rice, spaghetti	Potato chips, hominy
Soups	Unsalted cream soup made with milk allowance	Any other
Sweets	Pure sugar candy, honey jam, jelly, or marmalade made without sodium benzoate, molasses, sugar	Candy, except that listed under 'Foods Included
Vegetable	Any canned, cooked, or raw vegetables prepared without salt except those listed under 'Foods Excluded"	Vegetables prepared or canned with salt, frozen corn, peas or lima beans, beets, beet greens, celery, collards, kale and spinach
Miscellaneous	Chocolate, cocoa; herbs spices and vinegar unsalted nuts, popcorn	Catsup, chili sauce, gravy horseradish, prepared mustard, salted nuts, olives peanut butter, salted pickles, popcorn; relishes, salt

Sample Menu

Breakfast	
Fruit Juice or Fruit with sugar	1 large serving (See Lists 1 and 3)
Cereal	1 serving (See List 4)
Eggs	2
Bread or Toast, unsalted	2 slices
Butter, unsalted	as desired
Jelly	1 tablespoon
Milk	1 cup
Coffee or Tea	as desired
Sugar	2 tablespoons
10 A.M.	
Fruit Juice or Fruit with sugar	1 large serving (See Lists 1 and 3)
Noon Meal	
Meat, Fish, or Poultry	4 ounces (See List 5)
Potato or Substitute	1 serving (See List 4)
Vegetable	1 serving (See List 2)
Salad (vegetable or fruit)	1 serving (See Lists 2 and 3)
Fruit with sugar	1 large serving (See List 3)
Bread, unsalted	1 slice
Butter, unsalted	as desired
Jelly	1 tablespoon
Milk	1 cup
3 P.M.	
Milk	1 cup
Low sodium protein supplement	2 tablespoons
Sugar	1 tablespoon
Evening Meal	
Meat, Fish, or Poultry	4 ounces (See List 5)
Potato or Substitute	1 serving (See List 4)
Vegetable	1 serving (See List 2)
Salad (vegetable or fruit)	1 serving (See Lists 2 and 3)
Fruit with sugar	1 large serving
Bread, unsalted	1 slice
Butter, unsalted	as desired
Jelly	1 tablespoon
Milk	1 cup
8 P.M.	
Sandwich — Meat	2 ounces
Bread, unsalted	2 slices
Fat	as desired

Exchange List

Beverage Exchanges — List 1	
Milk	4 cups
Coffee or Tea	as desired

Vegetable Exchanges — List 2 (one half cup is a serving)

Asparagus—6 medium stalks	Mushrooms
Broccoli	Okra
Brussels Sprouts	Onions
Cabbage	Peas, green (not frozen)
Carrots	Pepper, green
Cauliflower	Radishes
Chicory	String beans
Cucumbers	Squash
Endive	Tomatoes
Escarole	Watercress
Eggplant	Pumpkin
Greens turnip	Rutabagas
Lettuce	Turnips

Fruit Exchanges — List 3 (one-half cup is an average size serving, one cup is a large serving)

Any fresh or canned Fruit Juice, except Tomato and V 8 Juice
Any fresh frozen, or canned Fruit.

Bread Exchanges — List 4

Bread, unsalted	1 slice
Cream or Wheat, regular	½ cup
Oatmeal, regular	½ cup
Pettijohns	½ cup
Ralstons, instant	½ cup
Puffed Rice or Puffed Wheat	¾ cup
Shredded Wheat	1 small biscuit
Rice, grits, spaghetti, noodles, macaroni	½ cup
Beans, Lima (not frozen)	½ cup
Beans, Navy, dried	½ cup
Corn	½ cup
Peas, black-eyed	½ cup
Potatoes, sweet	½ medium
Potatoes, white	1 small

Meat Exchanges — List 5

Meat and Poultry (beef, lamb, liver, veal, chicken, turkey, sweetbreads, and fresh pork)	4 ounces
Fish, fresh water	4 ounces
Oysters	20 small
Salmon or Tuna (water pack and without salt)	1 cup
Eggs	4

Fat Exchanges — List 6

Butter, unsalted
Oil, cooking, unsalted
Mayonnaise or French Dressing (made without salt)
Nuts, unsalted
Avocado

Miscellaneous Exchanges — List 7

These foods may be used as desired, cocoa herbs, spices, vinegar, pepper, sugar, sugar candies, plain chocolate, honey, jam and jelly (without sodium preservatives), plain gelatin and lemon

INSTRUCTIONS TO PATIENT

Be sure to eat all foods as listed on your meal plan

Include in between meal nourishments unless they interfere with your appetite for the following meal

Limit low caloric foods such as tea, coffee, excess roughage or high fiber foods

It is recommended that you use simply prepared meats and vegetables

Use fried or greasy goods in moderation

Use fresh or frozen vegetables or those canned without salt

Prepare all foods without the addition of salt

Use unsalted bread and unsalted butter

Use liberal servings of meat, fish, poultry, milk, concentrated sweets such as jelly, sugar, and hard candies

Keep regular hours

MINIMAL SODIUM-RESTRICTED DIET

In the event that further restriction of sodium in the diet is advisable in the treatment of patients with hepatic diseases and ascites and edema, this diet may be used It provides a maximum of 0 4 gm and an average of 0.3 gm of sodium daily (750 to 1,000 mg. NaCl), and adequate amounts of calories, protein, carbohydrate, minerals and vitamins. In the event that more protein and calories are advisable, this diet should be supplemented by a low sodium preparation such as Gevral®, low sodium milk (Lonalac®), or Sustagen®

APPROXIMATE COMPOSITION

Calories	2,500
Protein	106 gm
Carbohydrate	300 gm
Fat	100 gm
Calcium	0 96 gm
Iron	13 70 mg
Phosphorus	1 544 gm
Vitamin A	16,358 I U
Thiamine	1 714 mg
Riboflavin	1 853 mg
Niacin	20 64 mg
Ascorbic acid	108 mg
Vitamin D	86 I U
Sodium	0 306 mg
Potassium	4 0 mg (estimated)

FOODS INCLUDED

Beverage	Coffee, tea and Lonalac (dialyzed milk).
Bread	Unsalted bread
Cereal	Cereals cooked without salt, cream of wheat, oatmeal, wheatena, grits prepared cereals, puffed rice, puffed wheat and shredded wheat
Dessert	Gelatin desserts
Egg	1 daily
Fat	Unsalted butter, pure vegetable oils and fat, heavy cream
Fruit	Any — cooked, canned, or raw
Meat	Two medium servings daily (3 ozs each): beef, chicken, fresh fish, oysters, lamb, liver, fresh pork, turkey and veal
Potato	White potato, sweet potato, macaroni, spaghetti, rice, noodles and grits All prepared without salt
Vegetables	Most raw, frozen vegetables and those canned without salt All prepared without salt
Miscellaneous	Cocoa, herbs, spices, vinegar, unsalted nuts, pepper, sugar candies, plain chocolate, honey, jam, jelly and sugar

FOODS OMITTED

Beverage	Milk buttermilk
Bread	Bread or crackers made with baking powder soda, milk, eggs or salt
Cereal	Any others than those listed as allowed
Cheese	All
Dessert	Desserts made with eggs, milk, baking powder or baking soda
Fat	Salted butter or margarine, bacon or ham fat
Fruits	Fruits dried with sodium benzoate
Meat	Salted pickled, smoked, brined or canned meats fish shrimp or glandular meats except liver
Potato or Sub	Potato chips hominy
Soups	All, except an all-vegetable soup without meat or broth
Vegetables	Celery, frozen lima beans and peas, beets, kale, spinach, vegetables canned with salt
Miscellaneous	Pickles, olives, catsup, sauces, salad dressing, mutard, peanut butter, salt, horseradish, molasses, syrup, candies made with salt, salted butter or milk, laxatives or other medications containing sodium

SAMPLE MENU (*No Salt on the Tray*)

Breakfast	Dinner	Supper
Orange Juice	Roast Beef	Sliced Chicken
Oatmeal	Whipped Potatoes	Rice
Scrambled Egg	Carrots	String Beans
Toast (Unsalted)	Fresh Fruit Salad (No Dressing)	Sliced Tomato Salad (No Dressing)
Butter (Unsalted)	Canned Pears	Apple
Heavy Cream	Bread (Unsalted)	Bread (Unsalted)
Coffee	Butter (Unsalted)	Butter (Unsalted)
Sugar	Lonalac	Lonalac

Low Sodium Milk

Lonalac® Dried dialized milk (Mead, Johnson & Co)

Composition Dry

Calories	145	per oz (3¼ T)
Protein	27	
Fat	28	
Carbohydrates	38	
Sodium	.02	

Composition

The following table lists important nutrients in normal whole milk and Lo Sodium milk

Nutrients Per 100 Grams	*Regular Milk (Unprocessed)*	*Lo Sodium Milk*
Mg Sodium	50	5
Mg Potassium	140	250
Mg Calcium	125	110
Grams Milk Fat	3 7	3 7
Carbohydrates	4.8	4 8
Grams Proteins	3.5	3.5
Calories	68	68
Mg Thiamin (Vit B₁)	04	02
Mg Riboflavin (Vit B₂, G)	17	08

The loss of vitamins can readily be replaced in the diet if considered advisable and the potassium increase should not cause concern since the average dietary intake is 3 000 to 5 000 mg per day

HIGH-PROTEIN, HIGH-CARBOHYDRATE, LOW-FAT DIET IN THE TREATMENT OF PATIENTS WITH BILIARY CIRRHOSIS

It has been shown that restriction of fat in the diet is unnecessary in the treatment of diseases of the liver However, some patients with hepatitis or primary or secondary biliary cirrhosis have been made more comfortable by restricting their dietary fat They are particularly intolerant to fat and may complain of flatulent dyspepsia, bloating, abdominal distention, nausea and steatorrhea. These patients may have an abnormally increased fecal loss of fat and nitrogen and impaired absorption of the fat-soluble vitamins and calcium The diet tends to be unpalatable, and some patients may refuse this drastic restriction of fat [12] This diet may be similarly employed in the treatment of sprue or sprue-like syndromes Initially, this diet was proposed for the management of patients with primary or secondary biliary cirrhosis who have cutaneous xanthomata and increased amounts of cholesterol and phospholipids in the

blood. It was found that these lipid fractions remained unchanged in patients on this diet.

The diet should be fortified daily by one multivitamin capsule, 2 to 3 teaspoons of calcium lactate, and 5 mg. of aqueous vitamin K. The administration of 2 tablets of bile salts after each meal is beneficial in decreasing the steatorrhea and fatty intolerance.

FOODS INCLUDED AND EXCLUDED IN THE LOW-FAT DIETARY PROGRAM FOR LIVER DISEASE

Type of Food	*Foods Included*	*Foods Excluded*
Beverage	Fat free buttermilk, carbonated beverage, cereal beverage, coffee, tea, skim milk, include at least 1½ quarts of skim milk or fat free buttermilk—3 of which should be fortified with 4 tablespoons dried skim milk	Whole milk, alcoholic beverages
Bread	Any except those listed under "Foods Excluded" saltines, soda crackers	Any made with eggs or large amounts of fat
Cereal	Any	None
Dessert	Angel food cake, gelatine desserts, ices, sherbet made without whole milk, canned or fresh sweetened fruits	Desserts made with chocolate, cocoa, cream, egg yolks fats or whole milk
Fat	Butter or fortified margarine limited to 3 teaspoons per day	Cream
Fruit	Any except that listed under "Foods Excluded"	Avocado
Meat, Egg or Cheese	Lean beef, chicken, lamb, turkey, veal, (include at least 7 ounces of meat daily), fish, shell fish, dry cottage cheese, 2 eggs daily	Fat meat, fish or fowl, fish canned in oil, all cheese except dry cottage cheese
Potato or Substitute	Potato, rice, spaghetti, macaroni	Fried potatoes, potao chips
Soup	Clear fat free broth	Any soup made with cream, fat, or whole milk
Sweets	Candy except those listed under "Foods excluded," jam, jelly, marmalade, molasses, syrups, sugar.	Candy made with cream, chocolate, cocoa, fat or nuts
Vegetable	Any	None
Miscellaneous	Catsup, chili sauce, pickles, herbs, popcorn, salt, spices, vinegars	Gravy, nuts, olives, peanut butter, buttered popcorn, white or cream sauces

APPROXIMATE COMPOSITION

Calories	2,360
Protein	150 gm
Fat	40 gm
Carbohydrate	400 gm
Calcium	1 9 gm
Iron	19 mg
Phosphorus	2 0 gm
Vitamin A	5000 I U
Thiamin	1 4 mg
Riboflavin	3.5 mg
Niacin	20 mg
Ascorbic acid	150 mg

DIETARY PATTERN AND SAMPLE MENU

Breakfast
- Fruit or fruit juice, ½ cup
- Cereal ½ cup
- Eggs—2
- Bread—2 slices
- Butter—1 teaspoon
- Skim milk—1 cup
- Sugar—1 tablespoon
- Jelly—1 tablespoon

Dinner and Supper
- Broth—if desired
- Lean meat—3½ ounces
- Potato or substitute—½ cup
- Vegetable—½ cup
- Salad
- Dessert
- Skim milk—1 cup
- Bread—2 slices
- Butter—1 teaspoon
- Jelly—1 tablespoon

10 00 A M , 3 00 P M and Bedtime
1 cup skim milk fortified with 4 tablespoons of skim milk powder

HIGH-PROTEIN REDUCING DIET

This High-Protein Reducing Diet is an adequate diet including foods that are high in protein It is used primarily for patients with diseases of the liver who are also overweight The fat is kept as low as is compatible with maximum palatability and a high protein content Fried foods, gravies, sauces and rich desserts are to be avoided

APPROXIMATE COMPOSITION

Foods Allowed	*1,200 Calories*	*1 500 Calories*
Calories	1,250	1,500
Protein	156 gm	163 gm
Fat	56 gm	66 gm
Carbohydrate	116 gm	153 gm
Calcium	1.22 gm	1 85 gm
Iron	18 6 mg	19 3 mg
Phosphorous	1.57 gm	2 35 gm

Vitamin A	8,220 I. U.	9,525 I. U.
Thiamin	1.05 mg	1.36 mg
Riboflavin	2.60 mg	3.46 mg
Niacin	21.2 mg	27.0 mg
Ascorbic acid	149 mg	157 mg

Foods Allowed	*1,200*	*1,500*
Eggs	2	2
Meat, Fish, Poultry	2 large servings	2 large servings
Vegetable Group A	as desired	as desired
Vegetable Group B	1	1
Fruit	3	3
Milk	1½ pint Skim Milk	1 quart Skim Milk
Bread or Substitute	1	2
Butter or Substitute	1	3
Nutrient	12 tablespoons	10 tablespoons

SAMPLE MENU
(1,200 Calories)

Breakfast	Dinner	Supper
Orange Juice	Roast Beef au Jus (Large Serving)	Consomme
2 Scrambled Eggs	Parslied Carrots	Sliced Chicken (Large Serving)
½ Slice Toast	Broccoli	String Beans
Butter	Fresh Fruit Salad (No Dressing)	Apple
Coffee	Tea Lemon	Tea Lemon
10:00 A.M.	*2:00 P.M.*	*8:00 P.M.*
1 Glass Skim Milk with 4 Tablespoons Nutrient	1 Glass Skim Milk with 4 Tablespoons Nutrient	1 Glass Skim Milk with 4 Tablespoons Nutrient

HIGH-CALORIC LIQUID DIET

The High-Caloric Liquid Diet is a diet which may be found practical for a temporary period in older, edentulous, or ill patients with diseases of the liver, if the amounts of calories and protein are necessary. It may be inadequate in iron, vitamin A, thiamin and niacin, and should be supplemented by a therapeutic multivitamin daily.

APPROXIMATE COMPOSITION

Calories	3 000	
Protein	80	gm
Fat	115	gm
Carbohydrate	230	gm
Calcium	2	gm
Iron	10	mg
Phosphorus	2 02	gm
Vitamin A	2,500	I U
Thiamin	1 0	mg
Riboflavin	3 8	mg
Niacin	3 6	mg
Ascorbic Acid	130	mg

FOODS ALLOWED

Beverage	Fruit juices, coffee, tea, milk and milk drinks
Cereal Gruels	Cream of wheat and strained oatmeal
Dessert	Plain gelatin desserts, ice cream and sherbets
Fat	Butter, cream and margarine
Eggs	Raw eggs in beverage
Soup	Broth and strained cream soups with pureed vegetables
Miscellaneous	Salt and sugar

FOODS OMITTED

All foods that are not liquid at body temperatures, and limit low caloric foods as broths etc

SAMPLE MENU

Breakfast	Dinner	Supper
Orange Juice (Large Glass)	Strained Cream of Asparagus Soup	Strained Cream Soup
Strained Oatmeal Gruel	Peach Juice (Large Glass)	Grape Juice (Large Glass)
Coffee	Ice Cream	Jello
Cream	Milk and Cream	Milk and Cream
Sugar		
Milk		
10 00 A M	2 00 P M	8 00 P M
Chocolate Malted Milk with Ice Cream	Pineapple Juice	Eggnog with 2 eggs and one half Cream
	Jello	

SUGGESTED RECIPES FOR MILK DRINKS TO SUPPLEMENT ORAL CALORIC INTAKE IN PATIENTS WITH HEPATIC DISEASE

Eggnog (237 Calories)

1 Egg
2 Teaspoon Sugar
¾ Cup Milk
Vanilla to taste

(Ice Cream may be added if desired)
½ cup = 145 Calories (Vanilla)
General Milkshake (376 Calories)
Meritene® (Protein Supplement) Milk Shake (390 Calories)
16 tablespoon Meritene®
1 cup milk
2 Tablespoon General
2 Teaspoons Sugar
1 Cup Milk
Vanilla to taste
(Ice Cream may be added if desired)
Milk Fortified with Powdered Milk (272 Calories)
4 Tablespoons powdered non fat milk
1 Cup Milk
Protenum Drink (437 Calories)
6 Tablespoon Protenum
¾ cup Milk
(Ice Cream may be added if desired)
Whole milk, 1 glass (123 calories)
Fresh Orange Juice, 1 glass (80 calories)
PROTENUM® (Mead) Chocolate flavored powder made of non fat dry milk solids, Calcium caseinate and dextrose

Composition Dry	
Calories	30 per T
Protein	42
Fat	2 0
Carbohydrates	46

3½ T = 1 oz = 105 Calories
Standard Dilution is 1 T to 4 oz Milk

HIGH CALORIC, HIGH PROTEIN, LOW-SODIUM LIQUID DIET EMPLOYING PREPARED MILK POWDERS

Composition	Gevral® (Lederle) *Prot 60 Gm* *Whole Milk 1 qt* *Nonfat milk Po* *3 cups (405 gm)* *Waters qs 2,000 cc*	Sustagen® (Mead-Johnson) *900 gm*
Vitamin A	7,000 USP Units	5,000 Units
Vitamin D	520 USP Units	500 Units
Thiamine	6 7 mg	10 mg
Riboflavin	14.5 mg	10 mg
Niacin	20 mg	100 mg
Pyridoxine	3.5 mg	5 0 mg
Ca pantothenate	20 mg	40 mg
Folic acid	1 0 mg	2.5 mg

Vitamin B_{12}	26 mcg	4 mcg
Choline dihydrogen citrate	772 mg	500 mg (Bitartrate)
Inositol	900 mg	—
Ascorbic acid (C)	88 mg	500 mg
Rutin	25 mg	—
Vitamin E	10 I U	—
Intrinsic factor conc	1 0 mg	—
Calcium	7.2 gm	6.3 gm
Phosphorus	5 gm	4.5 gm
Ca caseinate (protein)	—	—
Iron	12.8 mg	15 mg
Fluorine	0 1 mg	—
Copper	1.0 mg	—
Iodine	0.5 mg	—
Potassium	3.5 gm	7 gm
Manganese	1 0 mg	—
Zinc	0.5 mg	—
Magnesium	116 0 mg	—
Boron	0 1 mg	—
Carbohydrate	273 gm	600 gm
Calories	2 351	3,500
Total Protein	217 gm	210 gm
Sodium	2 8 gm	1 9 gm
Fat	42 gm	3.3% (30 gm)

TUBE FEEDINGS

It may be necessary to prescribe nourishment in the form of gastric intubation to patients with hepatic diseases who have no appetite

(1) Sustagen® (Mead Johnson & Co) is made from powdered whole milk, non-fat milk solids, calcium caseinate, Dextri-Maltose®, dextrose, vitamins and iron. It is advisable to introduce a small polyethylene tube through the nose or mouth into the stomach, and administer Sustagen® at a rate of 5 to 10 cc /minute This tube is tolerated well by patients for days to a week If the flow of Sustagen® is increased, patients may suffer from nausea, vomiting, abdominal distention or diarrhea The physician should

specify the amount of calories and the volume of feeding for a twenty-four hour period

SUSTAGEN® TUBE FEEDINGS

Recipe	I	II.	II
Sustagen®	2 cups	2½ cups	3 cups
Sterile Water	enough to make 1 quart (1,000 c c)		
Nutritive Value			
Calories	1 150	1,469	1,750
Protein	70 gm	88 gm	105 gm
Fat	10 gm	13 gm	15 gm
Carbohydrate	200 gm	250 gm	300 gm
Sodium	600 mg	750 mg	1 750
Potassium	2 4 gm	3 0 gm	900 mg
Calcium	2 1 gm	2.5 gm	3 5 gm
Iron	5 mg	5 mg	3 1 mg
Vitamin A	1 670 I U	2 087 I U	7.5 mg
Vitamin D	167	208	2,500 I U
Ascorbic Acid	100 mg	125 mg	250 mg
Thiamin	3 3 mg	4 1 mg	150 mg
Riboflavin	3 3	4 1	5 mg
Niacin	33 3 mg	41.2 mg	5 0 mg
Vitamin B_{12} (crystalline)	1 4 mcg	1 8 mg	2 mcg
Folic Acid	0 8 mg	1 0 mcg	1.2 mcg
Pyridoxine Hydrochloride	1 7 mg	2 1 mg	2 5 mg
Calcium Panthothenate	14 mg	17.5 mg	20 mg
Choline Bitartrate	166 mg	208 mg	250 mg

Note To every quart of Sustagen® 2 5 gm of NaCl is added, unless otherwise specified

Sodium content per quart of feeding after NaCL is added	1,583 mg	1,733 mg	1,883 mg

TUBE FEEDING FOR PATIENTS IN HEPATIC COMA

The dietary treatment of hepatic coma should consist of a liquid, high-caloric with no protein content, administered by gastric intubation This diet may consist of. (1) 10 to 20 per cent glucose in water in the amount of 2,000 to 2,500 cc. per day (800 to 2,000 calories) (2) Formula glucose 400 gm., peanut oil 100 cc, acacia q s to emulsify, water to 1 liter

Approximate Composition	
Calories	2,500
Protein	0
Carbohydrate	328 gm
Fat	110 gm

(3) Lipomul® (Upjohn) (4 calories/cc., an emulsion, 40 per cent fat (36% per cent peanut oil and 1 per cent coconut oil) and 10 per cent dextrose) or Ediol® (5 calories per cc., 50 per cent fat and 12.5 per cent carbohydrate).

250 cc. Lipomul®
2,000 cc. 10 per cent glucose

Approximate Composition	
Calories	1,800
Protein	0
Calories as Carbohydrates	1,000
Calories as Fat	800

These high-caloric, high-fat, no-protein feedings may produce nausea, vomiting, abdominal distention and diarrhea. If the patient awakens from coma, protein beginning with 20 gm. should be administered by intra-gastric drip, and increments of 10 gm. gradually increased up to 60 gm. per day provided no relapse has occurred. In order to secure sufficient caloric intake in this situation, diets containing 2,100 calories and 0.5 gm. of sodium may be prescribed. If 20 gm. protein are recommended daily, the amount of carbohydrate is 337 gm./day, and of fat, 75 gm./day. The same daily caloric and sodium intake may be kept stationary by increasing the content of protein to 40 gm., the carbohydrate to 326 gm., and the fat to 78 gm. (2,086 calories).

INTRAVENOUS FEEDINGS

In the event that additional supplement of calories, electrolytes, vitamins and fluid are necessary in the management of patients with diseases of the liver, the following intravenous preparation may be employed:

2,000 cc. 10 per cent glucose in water: 800 calories
2 cc. (5 mg.) vitamin K.
4 cc. vitamin B complex (Solu-B)®.

specify the amount of calories and the volume of feeding for twenty-four hour period.

SUSTAGEN® TUBE FEEDINGS

Recipe	I	II	II
Sustagen®	*2 cups*	2½ cups	3 cups
Sterile Water	enough to make 1 quart (1,000 c c)		
Nutritive Value			
Calories	1,150	1,469	1 750
Protein	70 gm	88 gm	105 gm
Fat	10 gm	13 gm	15 gm
Carbohydrate	200 gm	250 gm	300 gm
Sodium	600 mg	750 mg	1,750
Potassium	2 4 gm	3 0 gm	900 mg
Calcium	2 1 gm	2.5 gm	3.5 gm
Iron	5 mg	5 mg	3 1 mg
Vitamin A	1 670 I U	2,087 I U	7.5 mg
Vitamin D	167	208	2,500 I U
Ascorbic Acid	100 mg	125 mg	250 mg
Thiamin	3 3 mg	4 1 mg	150 mg
Riboflavin	3 3	4 1	5 mg
Niacin	33 3 mg	41.2 mg	5 0 mg
Vitamin B_{12} (crystalline)	1 4 mcg	1 8 mg	2 mcg
Folic Acid	0 8 mg	1 0 mcg	1.2 mcg
Pyridoxine Hydrochloride	1 7 mg	2 1 mg	2.5 mg
Calcium Panthothenate	14 mg	17.5 mg	20 mg
Choline Bitartrate	166 mg	208 mg	250 mg

Note To every quart of Sustagen® 2 5 gm of NaCl is added, unless otherwise specified

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The dietary treatment of hepatic coma should consist of a liquid, high-caloric with no protein content, administered by gastric intubation This diet may consist of: (1) 10 to 20 per cent glucose in water in the amount of 2,000 to 2,500 cc. per day (800 to 2,000 calories). (2) Formula glucose 400 gm , peanut oil 100 cc , acacia q s to emulsify, water to 1 liter.

1 tbsp sugar
1 tbsp 20% cream
coffee

Mid Morning	*Midafternoon*	*Bedtime*
⅔ cup pineapple juice with 1 tbsp lactose	Lemonade	1 glass orange juice
		2 unsalted crackers
		½ pad salt free butter

TEST DIET FOR STEATORRHEA AND FOR NITROGEN EXCRETION

This diet has been employed at the Mayo Clinic to determine the amount of fat and protein lost daily in the feces. It consists of 2,160 calories, 118 gm protein, 270 gm carbohydrate, and 102 gm. of fat. Collection of stools is aided by ingesting carmine markers seventy-two hours apart. The normal range of fecal fat (total lipid) is 1 8 to 6 7 gm per day (average 4 1) and that of fecal nitrogen, 0 8 to 2.5 gm. per day (average 1 7) This diet has been found beneficial in determining fecal fat and nitrogen loss in biliary cirrhosis [19,20]

VITAMINS

Standard vitamin formula listed in the Pharmacopoeia of the United States of America (U S P XIV) usually contain [10]

Ascorbic Acid (vitamin C) 75 mg
Calcium pantothenate 2 mg (estimated requirement)
Folic 8V
Pyridoxine unknown
Folic Acid 0 1 0.2 mg (estimated requirement)

It is recommended that patients who are receiving intravenous alimentation be prescribed vitamins at least in the amounts specified above. Despite unsatisfactory evidence that vitamins are beneficial for patients with diseases of the liver in the absence of avitaminosis, it has been the custom to administer vitamins orally in superfluous amounts [4]

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The following may also be added: potassium chloride, calcium chloride, 1 to 2 ampoules of 50 per cent glucose (1 ampoule supplies 200 calories) and antibiotics Isotonic sodium chloride should be substituted for water if edema or ascites are absent. The amount of fluid and electrolytes administered will depend upon the biochemical deficit

20 GM PROTEIN, 75 GM FAT, 337 GM CARBOHYDRATE, 0.5 GM SODIUM AND 2,100 CALORIC DIET

Breakfast
- 8 ozs orange juice
- 1 teasp lactose
- 1 cup salt free cereal
- 1 tbsp 20% cream
- 1 glass *Lanolac*® milk
- 1 slice salt free toast
- 1 pad salt free butter
- 1 tbsp sugar
- coffee

Lunch
- ½ cup salt-free tomatoe juice
- Vegetable-Plate
  - ½ cup salt free mashed potatoe
  - ½ cup salt free beans
  - ½ cup salt free squash
  - 1 tbsp corn oil
- Vinegar
- 1 slice salt free bread
- 1 pad salt free butter
- 2 teasp jam
- 1 baked banana with
  - 1 teasp sugar,
  - 1 teasp peanut oil
  - and lemon juice
- 1 tbsp 20% cream
- 1 teasp sugar
- coffee

Dinner
- ½ cup baked rice
- 1 peach with 1 tbsp corn syrup and 2 teasp sugar
- 1 slice salt free bread
- 1 pad salt-free butter
- jello
- 1 tbsp 20% cream
- 2 teasp sugar

Mid Morning
- 6 ounces apricot juice
- 1 tbsp lactose

Mid-Afternoon
- ⅔ glass of gingerale
- lime sherbet

Bedtime
- ⅔ cup pineapple juice with teasp lactose

10 GM PROTEIN, 74 GM FAT, 326 GM CARBOHYDRATE, 0.5 GM SODIUM, 2 066 CALORIC DIET

Breakfast
- 1 glass (8 oz) orange juice
- 1 cup unsalted cereal
- 2 tbsp 20% cream
- 1 slice salt free toast
- ½ pad salt-free buttter
- 1 tbsp jam
- grapefruit
- 1 tbsp sugar
- coffee

Lunch
- 1 cup salt free tomatoe juice
- 1 unsalted egg omelet
- 1 unsalted baked potatoe
- ½ cup unsalted green beans
- 1 slice unsalted bread
- 1 pad unsalted butter
- ½ broiled grapefruit with 1 tbsp lactose

Dinner
- 1 serving unsalted sliced chicken
- 1 unsalted mashed potatoe
- ½ cup unsalted asparagus
- 1 slice unsalted bread
- ½ pad unsalted butter
- 1 baked apple
- 1 tbsp 20% cream
- 2 tbsp. sugar
- coffee

1 tbsp sugar
1 tbsp 20% cream
coffee

Mid Morning	*Midafternoon*	*Bedtime*
⅔ cup pineapple juice with 1 tbsp lactose	Lemonade	1 glass orange juice 2 unsalted crackers ½ pad salt free butter

TEST DIET FOR STEATORRHEA AND FOR NITROGEN EXCRETION

This diet has been employed at the Mayo Clinic to determine the amount of fat and protein lost daily in the feces It consists of 2,460 calories, 118 gm protein, 270 gm carbohydrate, and 102 gm of fat. Collection of stools is aided by ingesting carmine markers seventy two hours apart The normal range of fecal fat (total lipid) is 1 8 to 6.7 gm per day (average 4 1) and that of fecal nitrogen, 0 8 to 2.5 gm per day (average 1 7) This diet has been found beneficial in determining fecal fat and nitrogen loss in biliary cirrhosis [19,20]

VITAMINS

Standard vitamin formula listed in the Pharmacopoeia of the United States of America (U S P. XIV) usually contains[10]

Vitamin A 5,000 I U

[illegible]

Pyridoxine unknown
Folic Acid 0 1 0.2 mg (estimated requirement)

It is recommended that patients who are receiving intravenous alimentation be prescribed vitamins at least in the amounts specified above Despite unsatisfactory evidence that vitamins are beneficial for patients with diseases of the liver in the absence of avitaminosis, it has been the custom to administer vitamins orally in superfluous amounts [4]

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